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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Attorney Docket No.	RIB-011PR
First Named Inventor	Chen

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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TITLE OF THE INVENTION (280 characters max)

BIFUNCTIONAL HETEROCYCLIC DERIVATIVES AND METHODS OF MAKING AND USING THE SAME

ENCLOSED APPLICATION PARTS *(check all that apply)*

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PATENT
Attorney Docket No. RIB-011PR

BIFUNCTIONAL HETEROCYCLIC DERIVATIVES AND METHODS OF MAKING AND USING THE SAME

FIELD OF THE INVENTION

The present invention relates generally to the field of anti-infective, anti-proliferative, anti-inflammatory, and prokinetic agents. More particularly, the invention relates to a family of bifunctional compounds having both a macrolide-type antibiotic moiety and at least one other heterocylic moiety, that are useful as such therapeutic agents. The present invention further relates to processes for the preparation of such agents, to intermediates useful in their preparation, to the use of the therapeutic agents, and to pharmaceuticals compositions containing them.

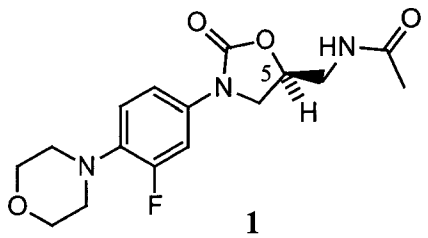
BACKGROUND

Since the discovery of penicillin in the 1920s and streptomycin in the 1940s, many new compounds have been discovered or specifically designed for use as antibiotic agents. It was once believed that infectious disease could be completely controlled or eradicated with the use of such therapeutic agents. However, such beliefs have been shaken by the fact that strains of cells or microorganisms resistant to currently effective therapeutic agents continue to evolve. In fact, virtually every antibiotic agent developed for clinical use has ultimately encountered problems with the emergence of resistant bacteria. *See, e.g.*, Gold, H.S. and Moellering, R.C., Jr., "Antimicrobial-Drug Resistance," *N. Engl. J. Med.*, **1996**, *335*, 1445-53.

For example, resistant strains of Gram-positive bacteria such as methicillin-resistant staphylocci, penicillin-resistant streptococci, and vancomycin-resistant enterococci have developed, and can cause serious and oftentimes fatal results for patients infected with such resistant bacteria. Also, bacteria that are resistant to the macrolide antibiotics, i.e. antibiotics based on a 14- to 16-membered lactone ring, have developed. Also, Gram-negative strains of bacteria such as H. influenze and M.catarrhalis have been identified.

Despite this problem of increasing antibiotic resistance, no new major classes of antibiotics have been developed for clinical use since the approval in 2000 of the oxazolidinone ring-containing antibiotic, N-[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-

oxazolidinyl]methyl acetamide, which is known as linezolid and is sold under the tradename Zyvox® (*see* compound 1).



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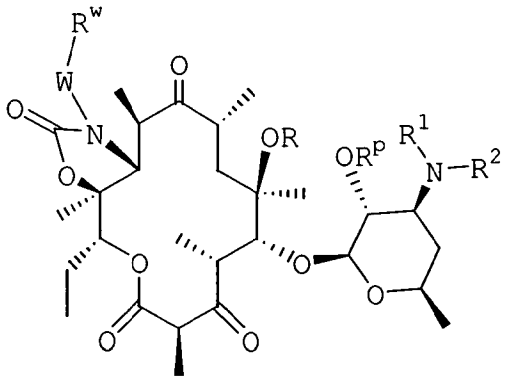
Linezolid was approved for use as an anti-bacterial agent active against Gram-positive organisms. Unfortunately, linezolid-resistant strains of organisms are already being reported. *See* Tsiodras *et al.*, *Lancet*, **2001**, *358*, 207; Gonzales *et al.*, *Lancet*, **2001**, *357*, 1179; Zurenko *et al.*, *Proceedings Of The 39th Annual Interscience Conference On Antibacterial Agents And Chemotherapy (ICAAC)*; San Francisco, CA, USA, September 26-29, 1999).

This problem of resistance is not limited to the area of anti-infective agents, because resistance has also been encountered with anti-proliferative agents used in cancer chemotherapy. Therefore, the need exists to develop new anti-infective and anti-proliferative agents that are both effective against resistant bacteria and strains of cells and against which bacteria and strains of cells are less likely to develop resistance.

Because linezolid is both a clinically effective and commercially significant anti-microbial agent, investigators have been working to develop other effective linezolid derivatives. Research has indicated that the oxazolidinone ring is essential for linezolid activity. The literature commonly describes molecules having small groups substituted at the C-5 of the oxazolidinone ring (indicated with a "5" in compound 1, above), and early structure-activity relationships suggested that compounds with larger groups at the C-5 position were less active as anti-bacterial agents. As a consequence, investigators have been reluctant to place large substituents at the C-5 position of oxazolidinone rings in anti-microbial agents.

U.S. Patent No. 6,034,069 depicts a series of 3'-N-modified 6-O-substituted erythromycin ketolide derivatives like that shown below. R, R^1, and R^2 are selected from a variety of groups, including aryl-alkoxy-heteroaryl-alkylene. R^P is H or a hydroxy protecting group. W is absent or is O, NH, or NCH_3. R^W is H or an optionally substituted alkyl group.



International Publication No. WO 99/63937 describes multi-binding compounds useful as antibiotics that are of the following formula:

$$(L)_p(X)_q$$

wherein L is selected from a macrolide antibiotic, an aminoglycoside, lincosamide, oxazolidinone, streptogramin, tetracycline, or another compound that binds to bacterial ribosomal RNA and/or to one or more proteins involved in ribosomal protein synthesis in the bacterium. P is an integer from 2-10. Q is an integer from 1-20. X is a linker.

The disclosure of International Publication No. WO 99/63937 was not the first to suggest attaching two antibiotics via a linker. Previously, U.S. Patent No. 5,693,791 described an antibiotic of the formula:

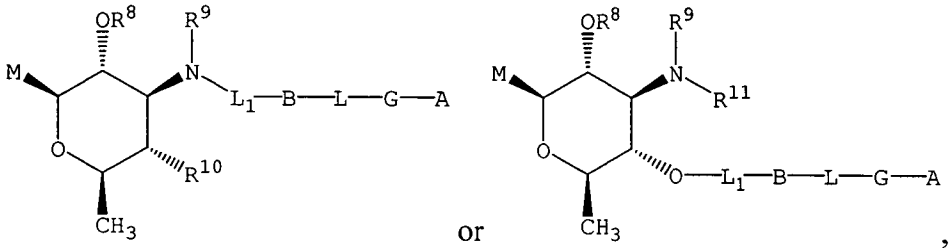
A-L-B

wherein A and B are antibiotics selected from sulfonamides, penicillins, cephalosporins, quinolones, chloramphenicol, erythromycin (i.e., a macrolide antibiotic), metronidzole, tetracyclines, and aminoglycosides. L is a linker formed from a difunctional linking agent.

Notwithstanding the foregoing, there is still an ongoing need for new anti-infective and anti-proliferative agents. Furthermore, because many anti-infective and anti-proliferative agents have utility as anti-inflammatory agents and prokinetic agents, there is also an ongoing need for new compounds useful as anti-inflammatory and prokinetic agents.

SUMMARY OF THE INVENTION

The invention provides a family of compounds useful as anti-infective agents and/or anti-proliferative agents, for example, chemotherapeutic agents, anti-microbial agents, anti-bacterial agents, anti-fungal agents, anti-parasitic agents, anti-viral agents, anti-inflammatory agents, and/or prokinetic (gastrointestinal modulatory) agents, having the formula:



or pharmaceutically acceptable salts, esters, or prodrugs thereof. The variables M, R^8, R^9, R^{10}, R^{11}, L_1, B, L, G, and A can be selected from the respective groups of chemical moieties later defined in the detailed description. More specifically, the variable M represents a 16-membered macrolide.

In addition, the invention provides methods of synthesizing the foregoing compounds. Following synthesis, a therapeutically effective amount of one or more of the compounds may be formulated with a pharmaceutically acceptable carrier for administration to a mammal for use as an anti-cancer, anti-microbial, anti-biotic, anti-fungal, anti-parasitic or anti-viral agent, or to treat a proliferative disease, an inflammatory disease or a gastrointestinal motility disorder. Accordingly, the compounds or the formulations may be administered, for example, via oral, parenteral, or topical routes, to provide an effective amount of the compound to the mammal.

The foregoing and other aspects and embodiments of the invention may be more fully understood by reference to the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of compounds that can be used as anti-proliferative agents and/or anti-infective agents. The compounds may be used without limitation, for example, as anti-cancer, anti-microbial, anti-bacterial, anti-fungal, anti-parasitic and/or anti-viral agents. Further, the present invention provides a family of compounds that can be used without limitation as anti-inflammatory agents, for example, for use in treating chronic inflammatory airway diseases, and/or as prokinetic agents, for example, for use in treating gastrointestinal motility disorders such as gastroesophageal reflux disease, gastroparesis (diabetic and post surgical), irritable bowel syndrome, and constipation.

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many

geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention.

1. Definitions

For the purposes of the present invention, the following definitions have been used throughout.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N). The present invention, in general, does not cover groups such as N-halo, S(O)H, and SO_2H.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^8) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^8, then said group may optionally be substituted with up to two R^8 groups and R^8 at each occurrence is selected independently from the definition of R^8. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are nitrogens in the compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of the present invention. Thus, all shown and claimed nitrogens are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-6} alkyl, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, and n-hexyl.

As used herein, "alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-6} alkenyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups.

As used herein, "alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-6} Alkynyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups.

As used herein, "cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-8} cycloalkyl is intended to include C_3, C_4, C_5, C_6, C_7, and C_8 cycloalkyl groups.

As used herein, "halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

As used herein, "alkoxy" is intended to mean an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy.

As used herein, "carbocycle" or "carbocyclic ring" is intended to mean, unless otherwise specified, any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, or 12-membered bicyclic or tricyclic ring, any of which may be saturated, unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (e.g., naphthyl and tetrahydronaphthyl) and spiro rings are also included.

As used herein, the term "heterocycle" or "heterocyclic" is intended to mean, unless otherwise stated, a stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, or 12-membered bicyclic or tricyclic heterocyclic ring which is saturated, unsaturated, or aromatic, and which consists of carbon atoms and one or more heteroatoms, e.g. 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen, and sulfur and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N\rightarrow O$ and $S(O)_p$, where p = 1 or 2). When a nitrogen atom is included in the ring it is either N

or NH, depending on whether or not it is attached to a double bond in the ring (i.e., a hydrogen is present if needed to maintain the tri-valency of the nitrogen atom). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

As used herein, the term "aromatic heterocyclic" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, or 12-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and one or more heteroatoms, e.g. 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen, and sulfur. In the case of bicyclic heterocyclic aromatic rings, only one of the two rings needs to be aromatic (e.g., 2,3-dihydroindole), though both may be (e.g., quinoline). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Spiro and fused rings are also included.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl,

indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic,

pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990), the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

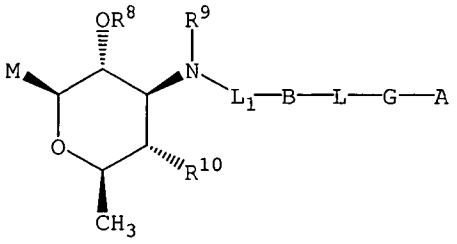
As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet

been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

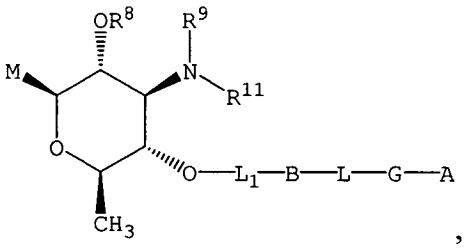
"Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination as an antiproliferative and/or anti-infective. "Therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective as an antiproliferative and/or anti-infective. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*:27-55, occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiproliferative and/or anti-infective effect, or some other beneficial effect of the combination compared with the individual components.

2. Compounds of the Invention

In one aspect, the invention provides compounds of the formula:



or



,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

A is selected from H, R^2, phenyl-R^2, and pyridyl-R^2, wherein the phenyl and pyridyl groups are substituted with 0-2 R^1 groups;

R^1, at each occurrence, is selected from H, F, Cl, Br, I, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $(CR^3R^3)_rCF_3$, $(CR^3R^3)_rCN$, $(CR^3R^3)_rNO_2$, $(CR^3R^3)_rNR^3R^3$, $(CR^3R^3)_rOR^3$, $(CR^3R^3)_rS(O)_pR^3$, $(CR^3R^3)_rC(O)R^3$, $(CR^3R^3)_rC(O)OR^3$, $(CR^3R^3)_rOC(O)R^3$, $(CR^3R^3)_rNR^3C(O)R^3$, $(CR^3R^3)_rC(O)NR^3R^3$, $(CR^3R^3)_rC(=NR^3)R^3$, $(CR^3R^3)_rNR^3C(O)NR^3R^3$, $(CR^3R^3)_rNR^3S(O)_pR^3$, $(CR^3R^3)_rS(O)_pNR^3R^3$,

$(CR^3R^3)_rNR^3S(O)_pNR^3R^3$, $(CR^3R^3)_r$-C_{3-10} saturated, unsaturated, or aromatic carbocycle substituted with 0-1 R^3 groups, and a $(CR^3R^3)_r$-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-3 R^3 groups;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, and 2;

R^2 is selected from R^4, C_{1-8} alkyl substituted with 0-4 R^4 groups, C_{2-8} alkenyl substituted with 0-4 R^4 groups, C_{2-8} alkynyl substituted with 0-4 R^4 groups, C_{3-12} carbocycle substituted with 0-4 R^4 groups, and 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-4 R^4 groups;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, phenyl, and benzyl;

alternatively, NR^3R^3 comprises a 3-6 membered saturated, unsaturated, or aromatic heterocycle containing the nitrogen atom to which the R^3 groups are attached and optionally containing one or more oxygen, nitrogen, and sulfur atoms;

B is a 5-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-2 carbonyl groups and 0-2 R^4 groups;

R^4, at each occurrence, is selected from H, =O, F, Cl, Br, I, C_{1-6} alkyl substituted with 0-3 R^6 groups, C_{2-6} alkenyl substituted with 0-3 R^6 groups, C_{2-6} alkynyl substituted with 0-3 R^6 groups, $(CR^3R^5)_rCF_3$, $(CR^3R^5)_rCN$, $(CR^3R^5)_rNO_2$, $(CR^3R^5)_rNR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rOR^6$, $(CR^3R^5)_rS(O)_p(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(O)(CR^3R^3)_tR^6$, $(CR^3R^5)_rOC(O)(CR^3R^3)_tR^6$, $(CR^3R^5)_rSC(O)(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(O)O(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3C(O)(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(O)NR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(O)NR^{4a}(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(=NR^3)(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(=NNR^{4a}R^{4a})(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(=NNR^3C(O)R^{4a})(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(=NOR^6)(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3C(O)O(CR^3R^3)_tR^6$, $(CR^3R^5)_rOC(O)NR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3C(O)NR^3(CR^3R^3)_tR^6$,

$(CR^3R^5)_rNR^3S(O)_p(CR^3R^3)_tR^6$, $(CR^3R^5)_rS(O)_pNR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3S(O)_pNR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_r$-C_{3-10} saturated, unsaturated, or aromatic carbocycle substituted with 0-3 R^6 groups, and $(CR^3R^5)_r$-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-3 R^6 groups;

alternatively, two R^4 groups may form $-O(CH_2)_sO-$;

R^{4a}, at each occurrence, is selected from H, C_{1-8} alkyl, C_{3-8} cycloalkyl, $(CH_2)_uOR^3$, and $(CH_2)_vNR^3R^3$;

alternatively, $NR^{4a}R^{4a}$ comprises a 5-6 membered saturated, unsaturated, or aromatic heterocycle containing the nitrogen atom to which the R^{4a} groups are attached and optionally containing one or more oxygen, nitrogen, and sulfur atoms, and substituted with 0-1 R^7 groups;

s, at each occurrence, is selected from 1, 2, 3, or 4;

t, at each occurrence, is selected from 0, 1, or 2;

u, at each occurrence, is selected from 1, 2, 3, 4, or 5;

v, at each occurrence, is selected from 0, 1, 2, or 3;

R^5, at each occurrence, is selected from H, C_{1-6} alkyl substituted with 0-3 R^7, C_{2-6} alkenyl substituted with 0-3 R^7, and C_{2-6} alkynyl substituted with 0-3 R^7;

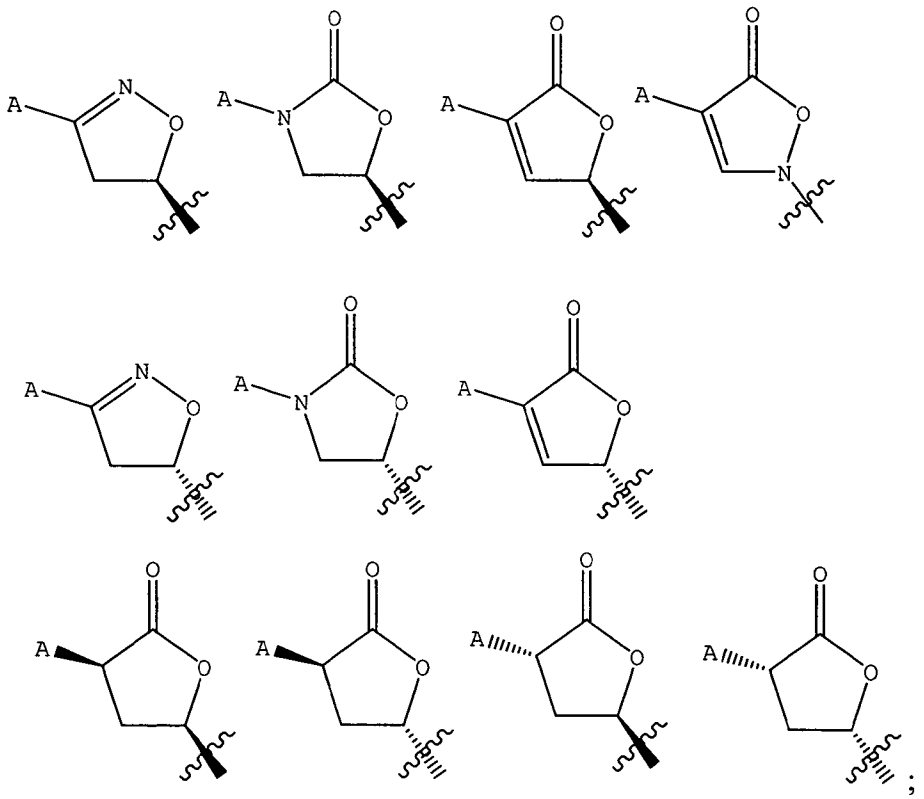
alternatively, CR^3R^5 comprises a carbonyl group;

R^6, at each occurrence, is selected from R^7, C_{1-6} alkyl substituted with 0-3 R^7 groups, C_{2-6} alkenyl substituted with 0-3 R^7 groups, C_{2-6} alkynyl substituted with 0-3 R^7 groups, $(CR^3R^5)_r$-C_{3-10} saturated, unsaturated, or aromatic carbocycle substituted with 0-3 R^7 groups, and $(CR^3R^5)_r$-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-3 R^7 groups;

R^7, at each occurrence, is selected from H, =O, F, Cl, Br, I, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CR^3R^3)_rCF_3$, $(CR^3R^3)_rCN$, $(CR^3R^3)_rNO_2$, $(CR^3R^3)_rNR^3R^3$,

$(CR^3R^3)_rOR^3$, $(CR^3R^3)_rS(O)_pR^3$, $(CR^3R^3)_rC(O)R^3$, $(CR^3R^3)_rC(O)OR^3$, $(CR^3R^3)_rOC(O)R^3$, $(CR^3R^3)_rNR^3C(O)R^3$, $(CR^3R^3)_rC(O)NR^3R^3$, $(CR^3R^3)_rC(=NR^3)R^3$, $(CR^3R^3)_rNR^3C(O)NR^3R^3$, $(CR^3R^3)_rNR^3S(O)_pR^3$, $(CR^3R^3)_rS(O)_pNR^3R^3$, $(CR^3R^3)_rNR^3S(O)_pNR^3R^3$, $(CR^3R^3)_r$-$C_{3\text{-}10}$ saturated, unsaturated, or aromatic carbocycle substituted with 0-1 R^3 groups, and $(CR^3R^3)_r$-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-3 R^3 groups;

G-A is selected from:

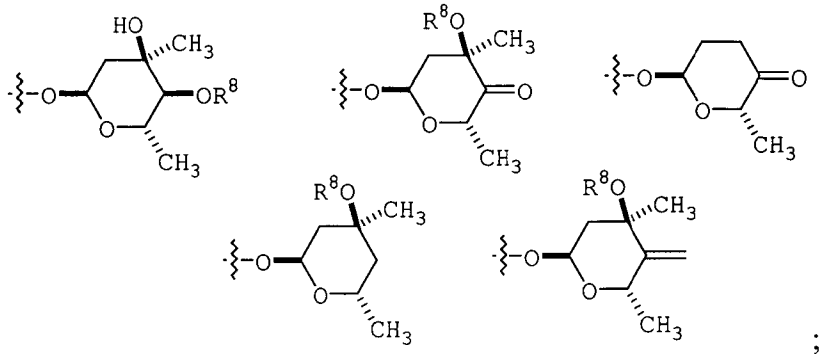


;

R^8, at each occurrence, is selected from H and C(O)-$C_{1\text{-}5}$ alkyl;

R^9 is selected from H, $C_{1\text{-}4}$ alkyl, and C(O)-$C_{1\text{-}5}$ alkyl;

R^{10} is OH or is selected from:



;

R^{11} is selected from H and C_{1-4} alkyl;

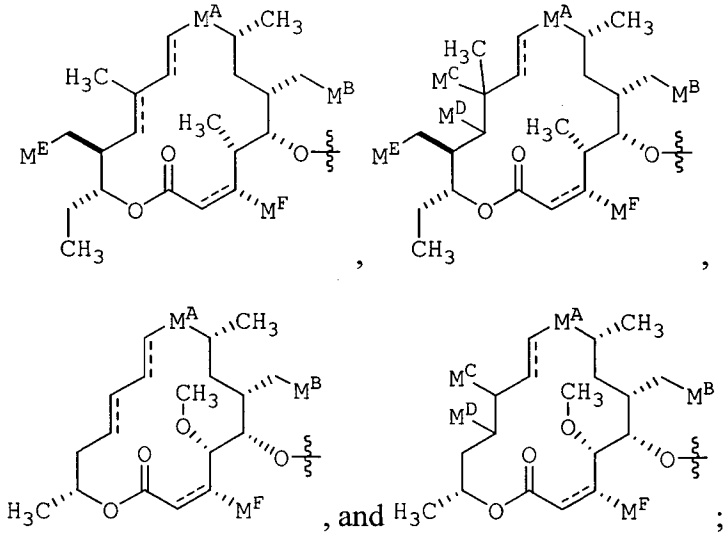
L is selected from $-CH_2-$, $-C(O)-$, $-C(S)-$, $-C(=NOR^{12})-$, $-CH_2CH_2-$, $-OCH_2-$, $-SCH_2-$, $-S(O)CH_2-$, $-S(O)_2CH_2-$, $-NR^{12}CH_2-$, $-C(O)CH_2-$, $-C(S)CH_2-$, and $-C(=NOR^{12})CH_2-$;

R^{12} is selected from H, C_{1-8} alkyl, C_{3-8} cycloalkyl, $(CH_2)_uOR^3$, and $(CH_2)_vNR^3R^3$;

L_1 is selected from $-CH_2-L_{1A}-$ and $-C(O)-L_{1A}-$;

L_{1A} is absent or is selected from C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl wherein 0-2 carbon atoms of L_{1A} are replaced by a heteroatom selected from oxygen, nitrogen, and sulfur, and L_{1A} is substituted with 0-1 carbonyl groups and 0-2 groups selected from C_{1-4} alkyl, OR^3, and NR^3R^3;

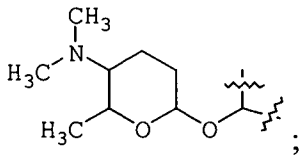
M is selected from:



;

wherein ----- is a carbon-carbon single bond or a carbon-carbon double bond;

M^A is selected from -CH_2-, -C(O)-, -C(O)-N(R^{13})-, -CH($NR^{13}R^{14}$)-, -C(=NOR^{13})-, -C(=N-$NR^{13}R^{14}$)-, -CH(-OR^{13})-, and



;

R^{13} is selected from H, C_{1-6} alkyl substituted with 0-2 R^4 groups, C_{2-6} alkenyl substituted with 0-2 R^4 groups, C_{2-6} alkynyl substituted with 0-2 R^4 groups, C_{6-10} saturated, unsaturated, or aromatic carbocycle substituted with 0-2 R^4 groups, and 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms, and substituted with 0-2 R^4 groups;

R^{14} is selected from H, C_{1-6} alkyl substituted with 0-4 R^4 groups, C_{2-6} alkenyl substituted with 0-4 R^4 groups, and C_{2-6} alkynyl substituted with 0-4 R^4 groups;

alternatively, $NR^{13}R^{14}$ comprises a 3-7 membered saturated, unsaturated, or aromatic heterocycle containing the nitrogen atom to which R^{13} and R^{14} are attached and optionally containing one or more oxygen, nitrogen, and sulfur atoms;

R^{15} is selected from H, C_{1-6} alkyl, phenyl, naphthyl, and 5-6 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms;

M^B is selected from C_{1-6} alkyl substituted with 0-2 R^{16} groups, C_{2-6} alkenyl substituted with 0-2 R^{16} groups, C_{2-6} alkynyl substituted with 0-2 R^{16} groups, -CHO, -C=N-$NR^{13}R^{14}$, -C=N-OR^{13}, -CH_2-$NR^{13}R^{14}$, -CH_2SR^{13}, and -CH_2OR^{13};

R^{16} is selected from C_{6-10} saturated, unsaturated, or aromatic carbocycle substituted with 0-2 R^4 groups, and 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-2 R^4 groups;

M^C is selected from H, OH, -OR^{13}, and -OC(O)-C_{1-5} alkyl substituted with 0-2 R^{16} groups;

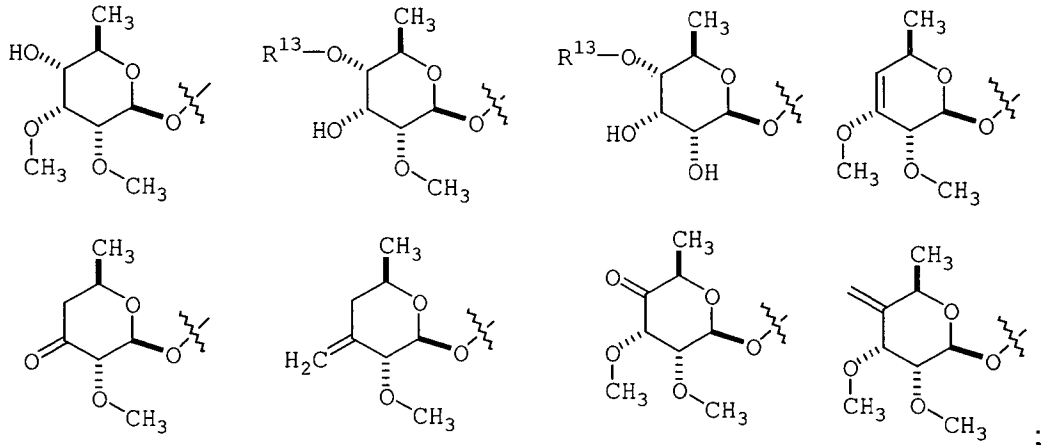
M^D is selected from H, OH, -OR^{13}, and -OC(O)-C_{1-5} alkyl substituted with 0-2 R^{16} groups;

alternatively, M^C and M^D taken together are -O- and form an epoxide ring with the two carbons to which they are respectively attached;

M^E is selected from H, OH, R^{17}, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkynyl, -O-C_{2-6} alkynyl, -C(O)-R^{13}, -C(O)-C_{1-6} alkylene-R^{13}, -C(O)-C_{2-6} alkenyl-R^{13}, -C(O)-C_{2-6} alkynyl-R^{13}, -C_{1-6} alkyl-X-R^{13}, -C_{2-6} alkenyl-X-R^{13}, and -C_{2-6} alkynyl-X-R^{13};

X is selected from -OC(O)-, -OC(O)O-, -OC(O)NR^{13}-, -C(O)NR^{13}-, -NR^{13}C(O)-, -NR^{13}C(O)O-, -NR^{13}C(O)NR^{14}-, -NR^{13}C(NH)NR^{14}-, and -$S(O)_p$;

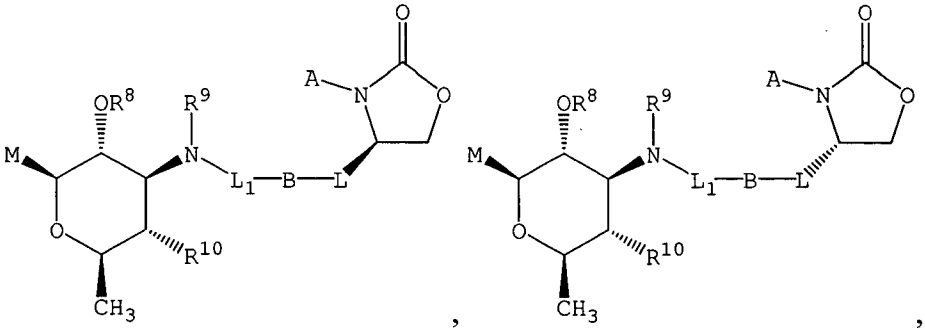
R^{17} is selected from:



; and,

M^F is selected from H, OH, -$NR^{13}R^{14}$, -C_{1-6} alkyl substituted with 0-2 R^{16} groups, -C_{2-6} alkenyl substituted with 0-2 R^{16} groups, -C_{2-6} alkynyl substituted with 0-2 R^{16} groups, -O-C(O)C_{1-5} alkyl, -O-R^{13}, -O-C_{1-6} alkyl substituted with 0-2 R^{16} groups, -O-C_{2-6} alkenyl substituted with 0-2 R^{16} groups, and -O-C_{2-6} alkynyl substituted with 0-2 R^{16} groups; provided that when M^F is attached to a double bond, it is H or -C_{1-6} alkyl substituted with 0-2 R^{16} groups.

Embodiments of the foregoing compounds include those having the formula:



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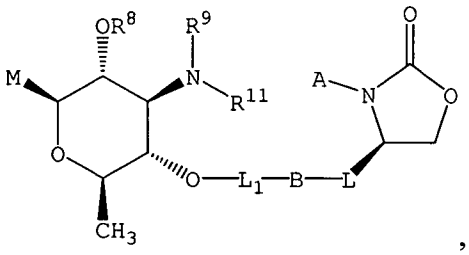
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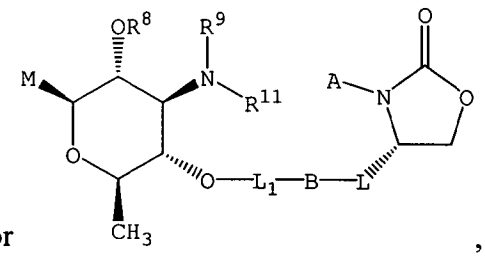
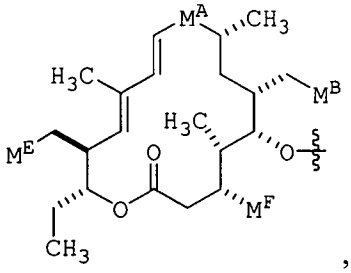

,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

B is substituted with 0-2 R^4 groups and is selected from: thiophene, furan, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5,-dihydrooxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1-tetrazol-5-yl, 2-tetrazol-5-yl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazolidine-2,4-dione, oxazolidine-2,4-dione, imidazolidine-2,4-dione, oxazolidin-2-one, thiazolidin-2-one, 3H-oxazol-2-one, 1,3-dihydro-imidazol-2-one, 1,3-dihydro-imidazole-2-thione, 2-thioxo-imidazolidin-4-one, and 4-thioxo-imidazolidin-2-one;

L_1 is selected from -C(O)CH=CH-, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(O)-$, $-CH_2CH_2C(O)-$, $-CH_2CH_2CH_2C(O)-$, $-C(O)CH_2-$, $-C(O)CH_2CH_2-$, $-C(O)CH_2CH_2CH_2-$, $-C(O)CH_2C(O)-$, $-C(O)CH_2CH_2C(O)-$, $-CH_2C(O)CH_2-$, $-CH_2C(O)CH_2CH_2-$, $-CH_2CH_2C(O)CH_2-$, and $-CH_2C(O)CH_2C(O)-$; and

M is selected from: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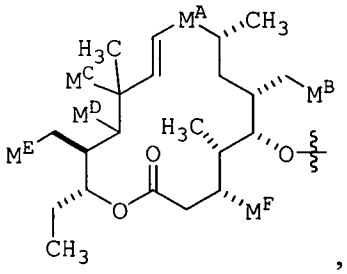
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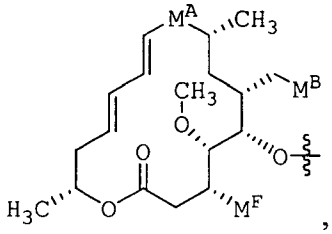
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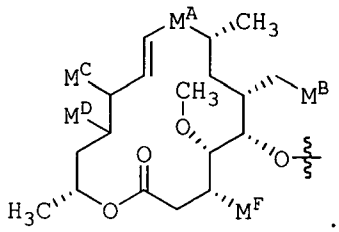
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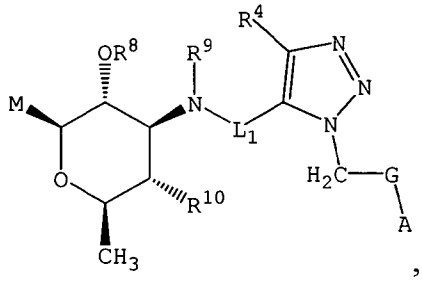
Other embodiments of the foregoing compounds include those having the formula: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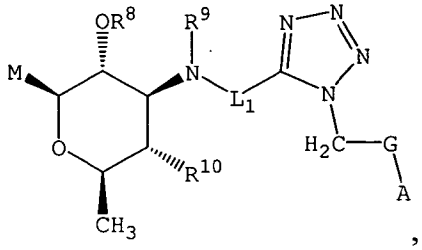
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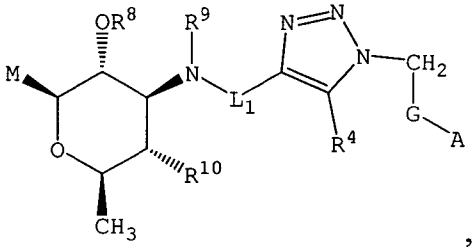
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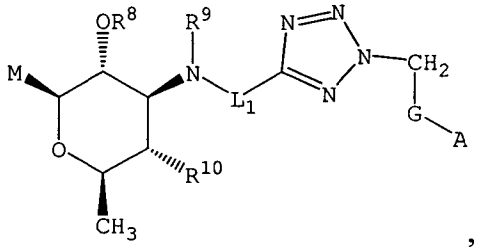
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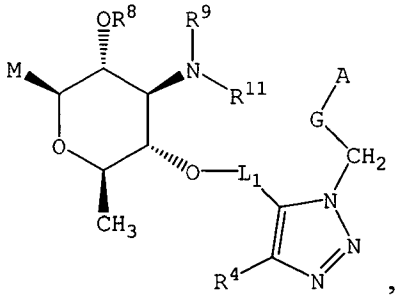
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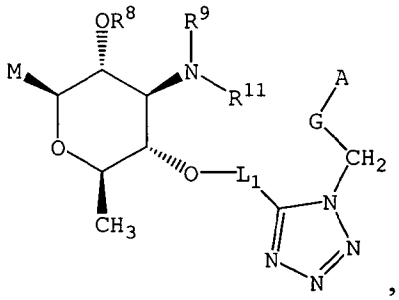
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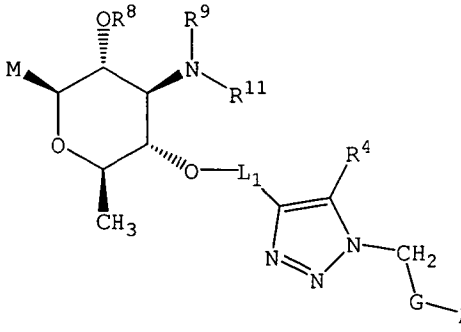
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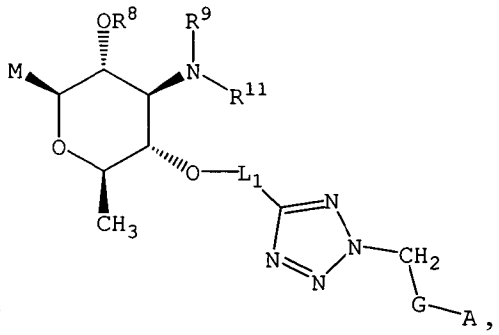
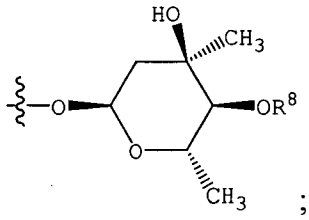

,

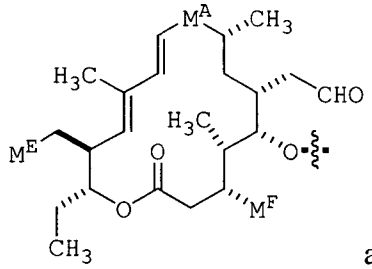
or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

R^{10} is selected from OH and:

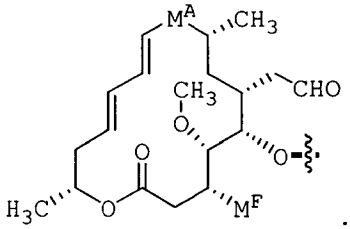


; and

M is selected from:

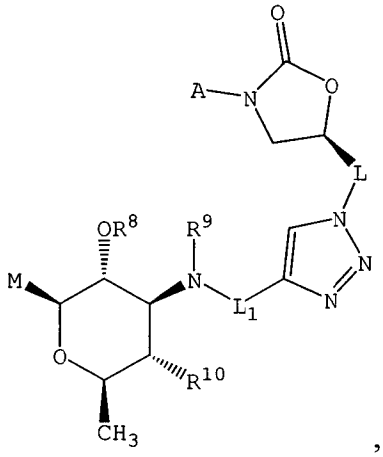


and

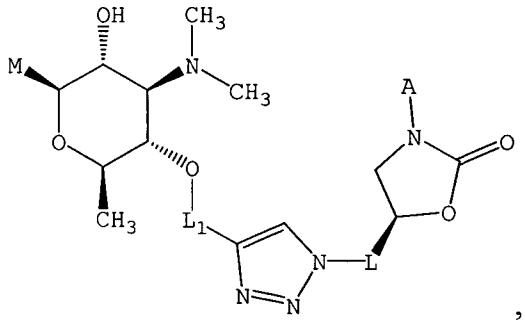


.

Still other embodiments of the foregoing compounds include those having the formula:



, or



,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

R^1, at each occurrence, is selected from H and F;

R^2 is selected from NR^3R^6, $C_{1\text{-}2}$ alkyl substituted with 1-2 R^4 groups, phenyl substituted with 0-2 R^4 groups, pyridyl substituted with 0-2 R^4 groups, morpholine substituted with 0-2 R^4 groups, imidazole substituted with 0-2 R^4 groups, and thiadiazole substituted with 0-2 R^4 groups;

R^4, at each occurrence, is selected from H, =O, F, Cl, Br, I, C_{1-4} alkyl, CF_3, CN, NO_2 , NR^3R^6, $CH_2NR^3R^6$, OR^6, CH_2OR^6, $S(O)_pR^6$, $C(O)R^6$, $C(O)OR^6$, $NR^3C(O)R^6$, $C(O)NR^3R^6$, $S(O)_pNR^3R^6$, C_{3-6} saturated, unsaturated, or aromatic carbocycle substituted with 0-3 R^6 groups, and a 3-6 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms, and substituted with 0-3 R^6 groups;

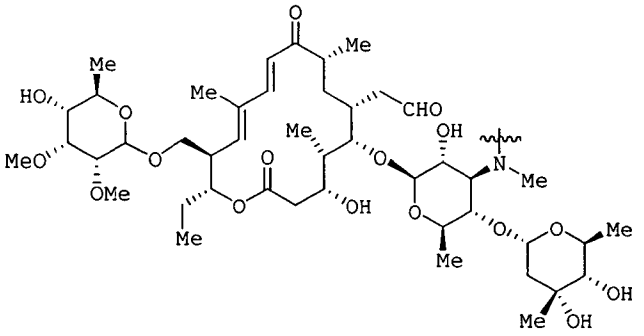
R^6, at each occurrence, is selected from H and CH_3; and

L_1 is selected from $-CH_2-$, $-CH_2CH_2-$, and $-CH_2CH_2CH_2-$.

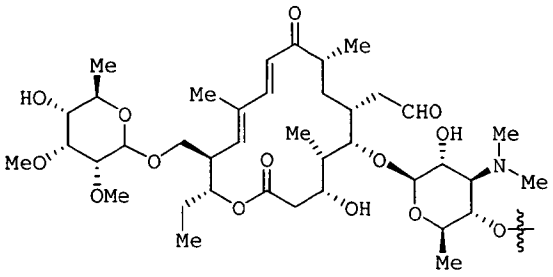
In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or more of the foregoing compounds and a pharmaceutically acceptable carrier. In yet another aspect, the invention provides a method for treating a microbial infection, a fungal infection, a viral infection, a parasitic disease, a proliferative disease, an inflammatory disease, or a gastrointestinal motility disorder in a mammal by administering effective amounts of the compounds of the invention or pharmaceutical compositions of the invention. In still another aspect, the invention provides methods for synthesizing any one of the foregoing compounds.

The present invention further provides a family of antibiotics comprising a macrolide moiety linked via a variable (preferably heteroaromatic) linker to at least a portion of an oxazolidinone-based antibiotic. These three groups correspond to the M, B, and G-A groups, respectively. Exemplary macrolides, linkers, and oxazolidinones useful in the synthesis of the antibiotics include, but are not limited to, the chemical moieties shown below.

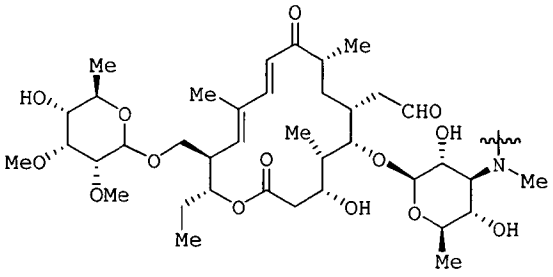
Macrolides



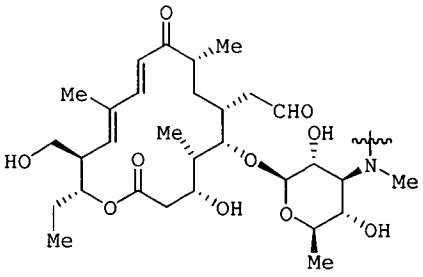
M1



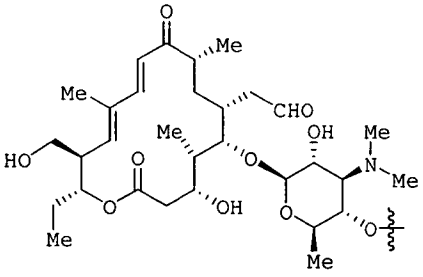
M2



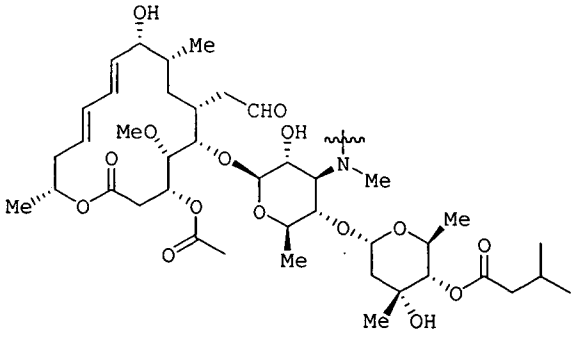
M3



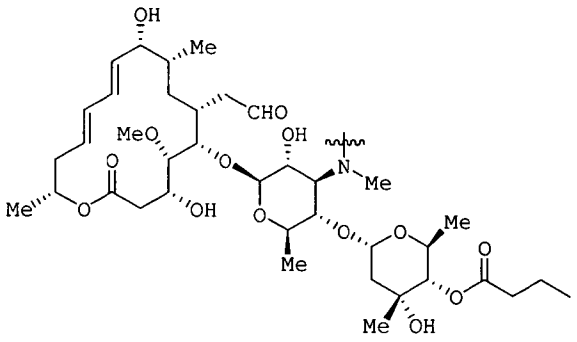
M4



M5

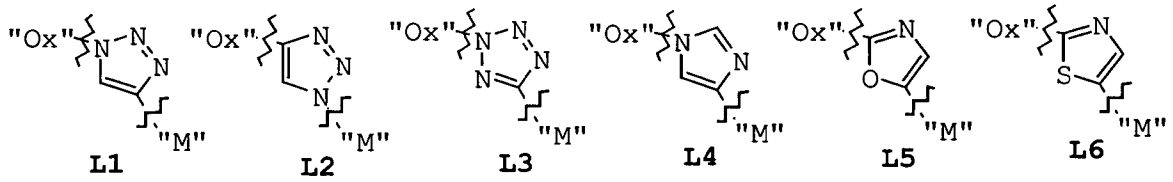


M6



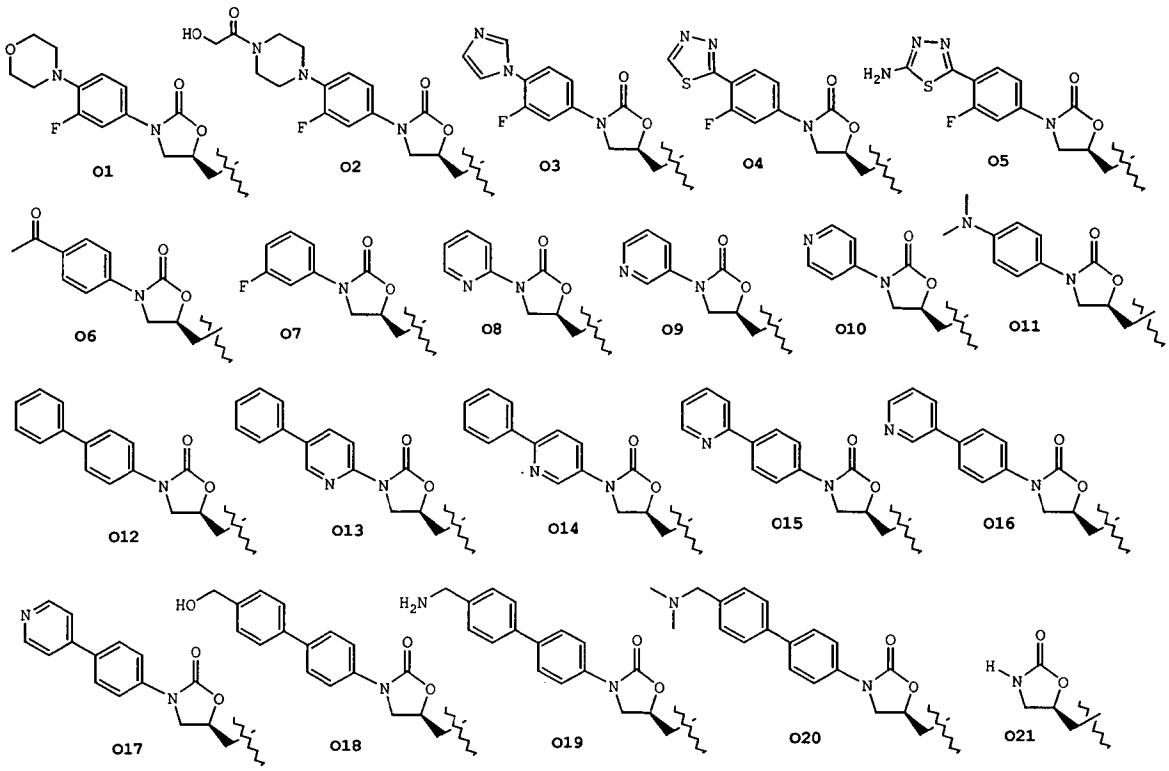
M7

Linkers

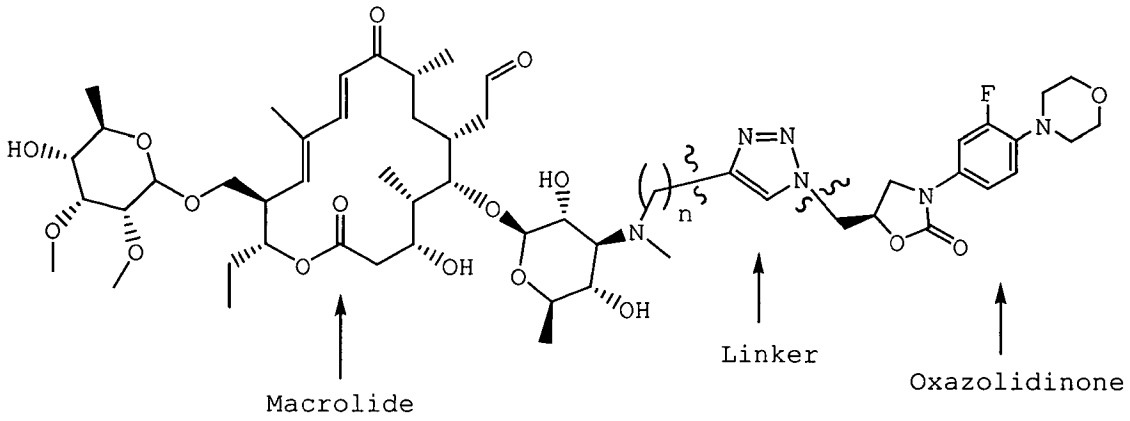


For the above linker groups, it should be understood that "M" and "Ox" are included to depict the orientation of the linker group with respect to the other structures that define the compounds of the invention. More specifically, "M" denotes the portion of the compound that includes the macrolide group and "Ox" denotes the portion of the compound that includes the oxazolidinone group.

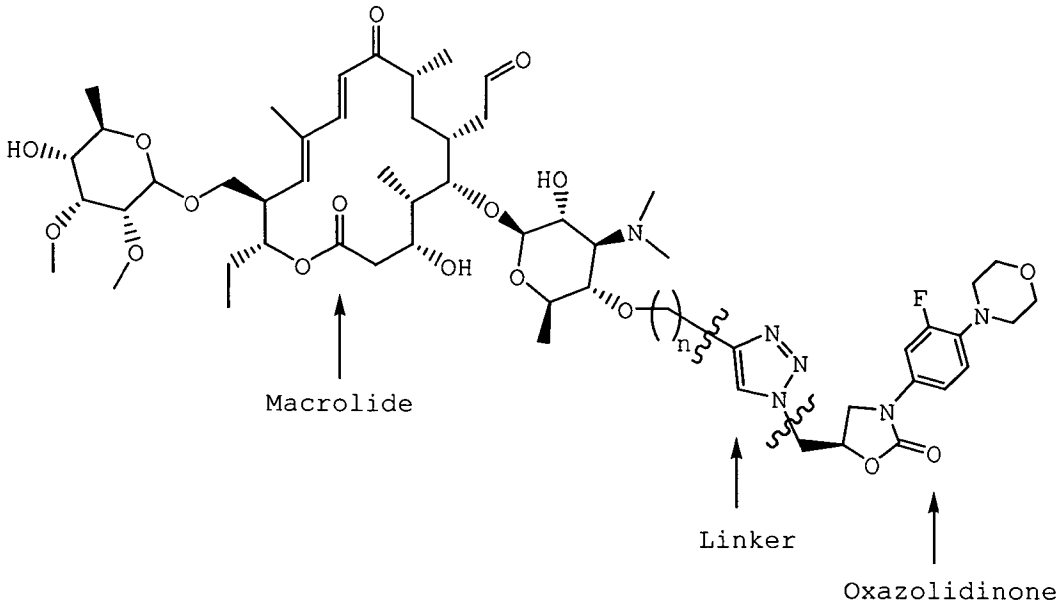
Oxazolidinones



For N-linked compounds, an exemplary scheme showing the linkage of a macrolide to an oxazolidinone group via a linker is shown below, where n can be 1, 2, or 3:



For O-linked compounds, an exemplary scheme showing the linkage of a macrolide to an oxazolidinone group via a linker is shown below, where n can be 1, 2, or 3:



The various macrolides may be N- or O-linked via the linkers to the oxazolidinone groups using conventional chemistries known in the art, such as those discussed below. By using the various combinations of chemical moieties provided, the skilled artisan may synthesize one or more of the exemplary compounds listed in Table 1. For each set of examples, the lower case letter designations, i.e., "**a**" through "**c**," denote the three compounds defined where n may vary from 1, 2, or 3. For example, as a guide to the following table, compound **E1a** is the n = 1 variant of the structure shown on the same row of the table. Similarly, **E1b** is the n = 2 variant, and **E1c** is the n = 3 variant.

Table 1

Example	Macrolide	Linker	Oxazolidinone
E1a-c	M1	L1	O1
E2a-c	M1	L1	O2
E3a-c	M1	L1	O3
E4a-c	M1	L1	O4
E5a-c	M1	L1	O5
E6a-c	M1	L1	O6
E7a-c	M1	L1	O7
E8a-c	M1	L1	O8
E9a-c	M1	L1	O9
E10a-c	M1	L1	O10
E11a-c	M1	L1	O11
E12a-c	M1	L1	O12
E13a-c	M1	L1	O13
E14a-c	M1	L1	O14

E15a-c	M1	L1	O15
E16a-c	M1	L1	O16
E17a-c	M1	L1	O17
E18a-c	M1	L1	O18
E19a-c	M1	L1	O19
E20a-c	M1	L1	O20
E21a-c	M1	L1	O21
E22a-c	M1	L2	O1
E23a-c	M1	L2	O2
E24a-c	M1	L2	O3
E25a-c	M1	L2	O4
E26a-c	M1	L2	O5
E27a-c	M1	L2	O6
E28a-c	M1	L2	O7
E29a-c	M1	L2	O8
E30a-c	M1	L2	O9
E31a-c	M1	L2	O10
E32a-c	M1	L2	O11
E33a-c	M1	L2	O12
E34a-c	M1	L2	O13
E35a-c	M1	L2	O14
E36a-c	M1	L2	O15
E37a-c	M1	L2	O16
E38a-c	M1	L2	O17
E39a-c	M1	L2	O18
E40a-c	M1	L2	O19
E41a-c	M1	L2	O20
E42a-c	M1	L2	O21
E43a-c	M1	L3	O1
E44a-c	M1	L3	O2
E45a-c	M1	L3	O3
E46a-c	M1	L3	O4
E47a-c	M1	L3	O5
E48a-c	M1	L3	O6
E49a-c	M1	L3	O7
E50a-c	M1	L3	O8
E51a-c	M1	L3	O9
E52a-c	M1	L3	O10
E53a-c	M1	L3	O11
E54a-c	M1	L3	O12
E55a-c	M1	L3	O13
E56a-c	M1	L3	O14
E57a-c	M1	L3	O15
E58a-c	M1	L3	O16
E59a-c	M1	L3	O17

E60a-c	M1	L3	O18
E61a-c	M1	L3	O19
E62a-c	M1	L3	O20
E63a-c	M1	L3	O21
E64a-c	M1	L4	O1
E65a-c	M1	L4	O2
E66a-c	M1	L4	O3
E67a-c	M1	L4	O4
E68a-c	M1	L4	O5
E69a-c	M1	L4	O6
E70a-c	M1	L4	O7
E71a-c	M1	L4	O8
E72a-c	M1	L4	O9
E73a-c	M1	L4	O10
E74a-c	M1	L4	O11
E75a-c	M1	L4	O12
E76a-c	M1	L4	O13
E77a-c	M1	L4	O14
E78a-c	M1	L4	O15
E79a-c	M1	L4	O16
E80a-c	M1	L4	O17
E81a-c	M1	L4	O18
E82a-c	M1	L4	O19
E83a-c	M1	L4	O20
E84a-c	M1	L4	O21
E85a-c	M1	L5	O1
E86a-c	M1	L5	O2
E87a-c	M1	L5	O3
E88a-c	M1	L5	O4
E89a-c	M1	L5	O5
E90a-c	M1	L5	O6
E91a-c	M1	L5	O7
E92a-c	M1	L5	O8
E93a-c	M1	L5	O9
E94a-c	M1	L5	O10
E95a-c	M1	L5	O11
E96a-c	M1	L5	O12
E97a-c	M1	L5	O13
E98a-c	M1	L5	O14
E99a-c	M1	L5	O15
E100a-c	M1	L5	O16
E101a-c	M1	L5	O17
E102a-c	M1	L5	O18
E103a-c	M1	L5	O19
E104a-c	M1	L5	O20

E105a-c	M1	L5	O21
E106a-c	M1	L6	O1
E107a-c	M1	L6	O2
E108a-c	M1	L6	O3
E109a-c	M1	L6	O4
E110a-c	M1	L6	O5
E111a-c	M1	L6	O6
E112a-c	M1	L6	O7
E113a-c	M1	L6	O8
E114a-c	M1	L6	O9
E115a-c	M1	L6	O10
E116a-c	M1	L6	O11
E117a-c	M1	L6	O12
E118a-c	M1	L6	O13
E119a-c	M1	L6	O14
E120a-c	M1	L6	O15
E121a-c	M1	L6	O16
E122a-c	M1	L6	O17
E123a-c	M1	L6	O18
E124a-c	M1	L6	O19
E125a-c	M1	L6	O20
E126a-c	M1	L6	O21
E127a-c	M2	L1	O1
E128a-c	M2	L1	O2
E129a-c	M2	L1	O3
E130a-c	M2	L1	O4
E131a-c	M2	L1	O5
E132a-c	M2	L1	O6
E133a-c	M2	L1	O7
E134a-c	M2	L1	O8
E135a-c	M2	L1	O9
E136a-c	M2	L1	O10
E137a-c	M2	L1	O11
E138a-c	M2	L1	O12
E139a-c	M2	L1	O13
E140a-c	M2	L1	O14
E141a-c	M2	L1	O15
E142a-c	M2	L1	O16
E143a-c	M2	L1	O17
E144a-c	M2	L1	O18
E145a-c	M2	L1	O19
E146a-c	M2	L1	O20
E147a-c	M2	L1	O21
E148a-c	M2	L2	O1
E149a-c	M2	L2	O2

E150a-c	M2	L2	O3
E151a-c	M2	L2	O4
E152a-c	M2	L2	O5
E153a-c	M2	L2	O6
E154a-c	M2	L2	O7
E155a-c	M2	L2	O8
E156a-c	M2	L2	O9
E157a-c	M2	L2	O10
E158a-c	M2	L2	O11
E159a-c	M2	L2	O12
E160a-c	M2	L2	O13
E161a-c	M2	L2	O14
E162a-c	M2	L2	O15
E163a-c	M2	L2	O16
E164a-c	M2	L2	O17
E165a-c	M2	L2	O18
E166a-c	M2	L2	O19
E167a-c	M2	L2	O20
E168a-c	M2	L2	O21
E169a-c	M2	L3	O1
E170a-c	M2	L3	O2
E171a-c	M2	L3	O3
E172a-c	M2	L3	O4
E173a-c	M2	L3	O5
E174a-c	M2	L3	O6
E175a-c	M2	L3	O7
E176a-c	M2	L3	O8
E177a-c	M2	L3	O9
E178a-c	M2	L3	O10
E179a-c	M2	L3	O11
E180a-c	M2	L3	O12
E181a-c	M2	L3	O13
E182a-c	M2	L3	O14
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E185a-c	M2	L3	O17
E186a-c	M2	L3	O18
E187a-c	M2	L3	O19
E188a-c	M2	L3	O20
E189a-c	M2	L3	O21
E190a-c	M2	L4	O1
E191a-c	M2	L4	O2
E192a-c	M2	L4	O3
E193a-c	M2	L4	O4
E194a-c	M2	L4	O5

E195a-c	M2	L4	O6
E196a-c	M2	L4	O7
E197a-c	M2	L4	O8
E198a-c	M2	L4	O9
E199a-c	M2	L4	O10
E200a-c	M2	L4	O11
E201a-c	M2	L4	O12
E202a-c	M2	L4	O13
E203a-c	M2	L4	O14
E204a-c	M2	L4	O15
E205a-c	M2	L4	O16
E206a-c	M2	L4	O17
E207a-c	M2	L4	O18
E208a-c	M2	L4	O19
E209a-c	M2	L4	O20
E210a-c	M2	L4	O21
E211a-c	M2	L5	O1
E212a-c	M2	L5	O2
E213a-c	M2	L5	O3
E214a-c	M2	L5	O4
E215a-c	M2	L5	O5
E216a-c	M2	L5	O6
E217a-c	M2	L5	O7
E218a-c	M2	L5	O8
E219a-c	M2	L5	O9
E220a-c	M2	L5	O10
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E222a-c	M2	L5	O12
E223a-c	M2	L5	O13
E224a-c	M2	L5	O14
E225a-c	M2	L5	O15
E226a-c	M2	L5	O16
E227a-c	M2	L5	O17
E228a-c	M2	L5	O18
E229a-c	M2	L5	O19
E230a-c	M2	L5	O20
E231a-c	M2	L5	O21
E232a-c	M2	L6	O1
E233a-c	M2	L6	O2
E234a-c	M2	L6	O3
E235a-c	M2	L6	O4
E236a-c	M2	L6	O5
E237a-c	M2	L6	O6
E238a-c	M2	L6	O7
E239a-c	M2	L6	O8

E240a-c	M2	L6	O9
E241a-c	M2	L6	O10
E242a-c	M2	L6	O11
E243a-c	M2	L6	O12
E244a-c	M2	L6	O13
E245a-c	M2	L6	O14
E246a-c	M2	L6	O15
E247a-c	M2	L6	O16
E248a-c	M2	L6	O17
E249a-c	M2	L6	O18
E250a-c	M2	L6	O19
E251a-c	M2	L6	O20
E252a-c	M2	L6	O21
E253a-c	M3	L1	O1
E254a-c	M3	L1	O2
E255a-c	M3	L1	O3
E256a-c	M3	L1	O4
E257a-c	M3	L1	O5
E258a-c	M3	L1	O6
E259a-c	M3	L1	O7
E260a-c	M3	L1	O8
E261a-c	M3	L1	O9
E262a-c	M3	L1	O10
E263a-c	M3	L1	O11
E264a-c	M3	L1	O12
E265a-c	M3	L1	O13
E266a-c	M3	L1	O14
E267a-c	M3	L1	O15
E268a-c	M3	L1	O16
E269a-c	M3	L1	O17
E270a-c	M3	L1	O18
E271a-c	M3	L1	O19
E272a-c	M3	L1	O20
E273a-c	M3	L1	O21
E274a-c	M3	L2	O1
E275a-c	M3	L2	O2
E276a-c	M3	L2	O3
E277a-c	M3	L2	O4
E278a-c	M3	L2	O5
E279a-c	M3	L2	O6
E280a-c	M3	L2	O7
E281a-c	M3	L2	O8
E282a-c	M3	L2	O9
E283a-c	M3	L2	O10
E284a-c	M3	L2	O11

E285a-c	M3	L2	O12
E286a-c	M3	L2	O13
E287a-c	M3	L2	O14
E288a-c	M3	L2	O15
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E291a-c	M3	L2	O18
E292a-c	M3	L2	O19
E293a-c	M3	L2	O20
E294a-c	M3	L2	O21
E295a-c	M3	L3	O1
E296a-c	M3	L3	O2
E297a-c	M3	L3	O3
E298a-c	M3	L3	O4
E299a-c	M3	L3	O5
E300a-c	M3	L3	O6
E301a-c	M3	L3	O7
E302a-c	M3	L3	O8
E303a-c	M3	L3	O9
E304a-c	M3	L3	O10
E305a-c	M3	L3	O11
E306a-c	M3	L3	O12
E307a-c	M3	L3	O13
E308a-c	M3	L3	O14
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E814a-c	M7	L3	O16
E815a-c	M7	L3	O17
E816a-c	M7	L3	O18
E817a-c	M7	L3	O19
E818a-c	M7	L3	O20
E819a-c	M7	L3	O21
E820a-c	M7	L4	O1
E821a-c	M7	L4	O2
E822a-c	M7	L4	O3
E823a-c	M7	L4	O4
E824a-c	M7	L4	O5

E825a-c	M7	L4	O6
E826a-c	M7	L4	O7
E827a-c	M7	L4	O8
E828a-c	M7	L4	O9
E829a-c	M7	L4	O10
E830a-c	M7	L4	O11
E831a-c	M7	L4	O12
E832a-c	M7	L4	O13
E833a-c	M7	L4	O14
E834a-c	M7	L4	O15
E835a-c	M7	L4	O16
E836a-c	M7	L4	O17
E837a-c	M7	L4	O18
E838a-c	M7	L4	O19
E839a-c	M7	L4	O20
E840a-c	M7	L4	O21
E841a-c	M7	L5	O1
E842a-c	M7	L5	O2
E843a-c	M7	L5	O3
E844a-c	M7	L5	O4
E845a-c	M7	L5	O5
E846a-c	M7	L5	O6
E847a-c	M7	L5	O7
E848a-c	M7	L5	O8
E849a-c	M7	L5	O9
E850a-c	M7	L5	O10
E851a-c	M7	L5	O11
E852a-c	M7	L5	O12
E853a-c	M7	L5	O13
E854a-c	M7	L5	O14
E855a-c	M7	L5	O15
E856a-c	M7	L5	O16
E857a-c	M7	L5	O17
E858a-c	M7	L5	O18
E859a-c	M7	L5	O19
E860a-c	M7	L5	O20
E861a-c	M7	L5	O21
E862a-c	M7	L6	O1
E863a-c	M7	L6	O2
E864a-c	M7	L6	O3
E865a-c	M7	L6	O4
E866a-c	M7	L6	O5
E867a-c	M7	L6	O6
E868a-c	M7	L6	O7
E869a-c	M7	L6	O8

E870a-c	M7	L6	O9
E871a-c	M7	L6	O10
E872a-c	M7	L6	O11
E873a-c	M7	L6	O12
E874a-c	M7	L6	O13
E875a-c	M7	L6	O14
E876a-c	M7	L6	O15
E877a-c	M7	L6	O16
E878a-c	M7	L6	O17
E879a-c	M7	L6	O18
E880a-c	M7	L6	O19
E881a-c	M7	L6	O20
E882a-c	M7	L6	O21

3. Synthesis of the Compounds of the Invention

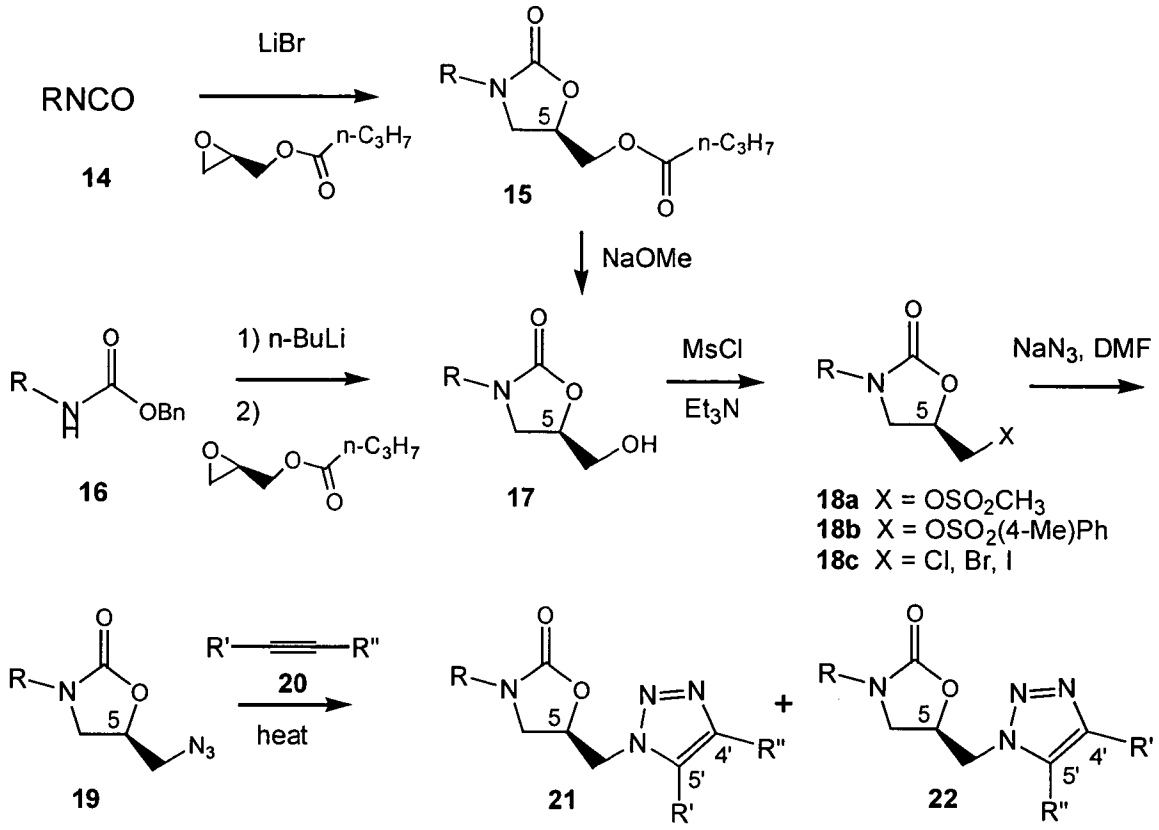
The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene, T.W.; Wuts, P.G.M. Protective Groups In Organic Synthesis, Third Edition, **1999**, John Wiley and Sons, New York, NY. All references cited herein are hereby incorporated in their entirety herein by reference for all purposes.

Scheme 1 illustrates the synthesis of oxazolidinones substituted at C-5 with 1,2,3-triazolylmethyl derivatives. Isocyanates **14** can react with lithium bromide and glycidyl butyrate at elevated temperatures to produce oxazolidinone intermediates of type **15** (Gregory *et al.*, *J.*

Med. Chem., **1989**, *32*: 1673). Hydrolysis of the resulting butyrate ester of compound **15** produces alcohol **17**. Alcohol **17** can also be synthesized from carbamates, such as the benzyl carbamate **16**. The carbamate nitrogen of compound **16** is deprotonated and alkylated with glycidyl butyrate to produce (after *in situ* hydrolysis of the butyl ester) hydroxymethyl derivative **17**. While the R enantiomer depicted throughout Scheme 1 generally is the most biologically useful derivative for antibacterial agents, compounds derived from either the R or the S enantiomer, or any mixture of R and S enantiomers, may be useful in the practice of the present invention and are included.

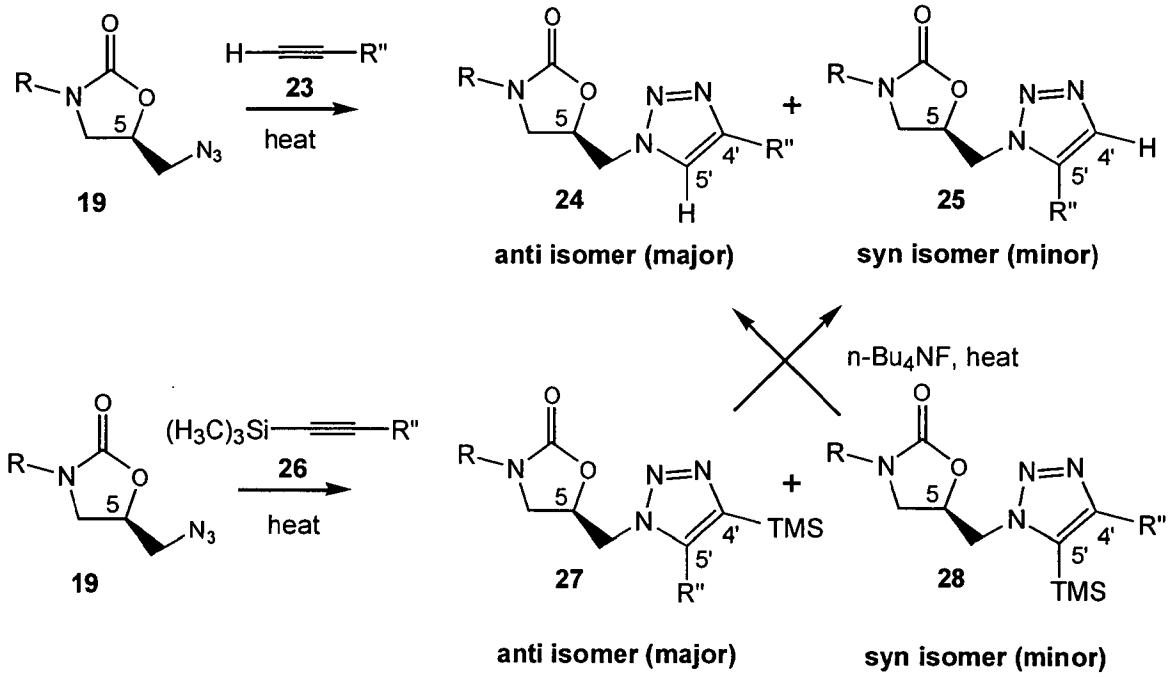
Alcohols **17** can be converted to useful intermediates such as mesylate **18a** (by treatment with methanesulfonyl chloride and triethylamine in an appropriate solvent) and azide **19** (by subsequent displacement of the mesylate by sodium azide in DMF). Azide **19** can also be produced from tosylate **18b** (or a brosylate or nosylate) or an alkyl halide of type **18c** (made from alcohol **17** via methods known to those skilled in the art). Azide **19** can be heated in the presence of substituted acetylenes **20** to produce C-5 substituted 1,2,3-triazolylmethyl oxazolidinone derivatives of type **21** and **22**. Alternative chemical conditions could also be employed by those skilled in the art to effect this transformation.

Scheme 1



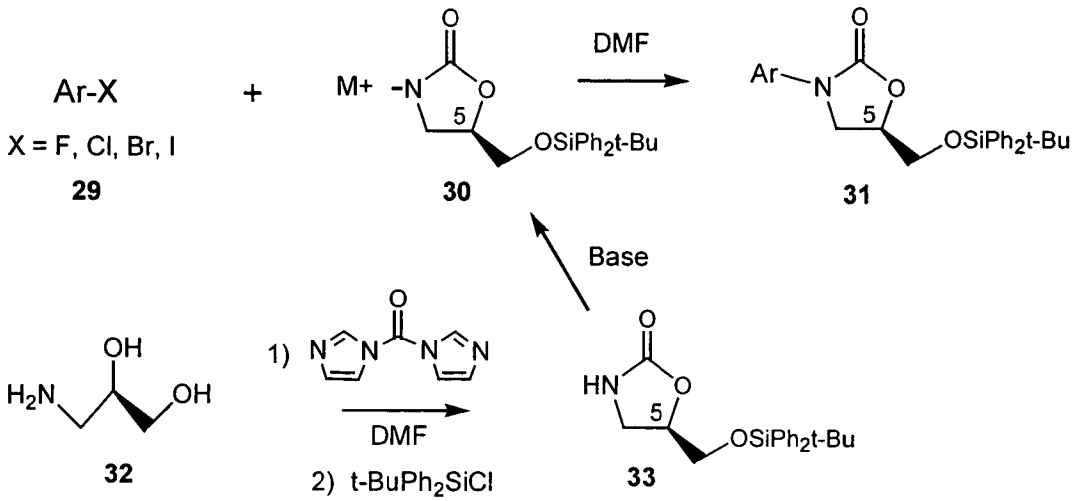
Unsymmetrical acetylene derivatives can react to produce a mixture of regioisomeric cycloaddition products, represented by **21** and **22**, and that the reaction conditions can be adjusted by processes known to those skilled in the art to produce more selectively one regioisomer or the other. For example, Scheme 2 depicts the reaction of mono-substituted acetylene **23** with azide **19** to produce two regioisomeric triazoles, **24** and **25**. The major isomer is most often the anti isomer **24** since the reaction leading to this product proceeds at a faster rate. Under certain circumstances, the more sterically disfavored syn isomer is also formed, but at an appreciably diminished rate. The addition of copper(I)iodide is a useful additive for this reaction, and often leads to increased proportions of the major "anti" adduct **24** (Tornoe, C.W. *et al.*, *J. Org. Chem.*, **2002**, *67*: 3057). Increased proportions of the minor isomer **25** may be produced by minor modification of the reaction scheme. Azide **19** can react with trimethylsilyl substituted acetylene **26** to produce the anti isomer **27** and the syn isomer **28**. Desilylation with tetrabutylammonium fluoride can produce triazole **24** and **25**, with increased proportions of **25** obtainable from the more abundant precursor triazole **27**.

Scheme 2



An alternate approach toward the synthesis of some of the compounds of the present invention is shown in Scheme 3. Aromatic halide **29**, when activated, can react with the anion derived from treatment of carbamate **33** with an appropriate base to produce 3-aryl substituted oxazolidinone derivatives **31** via nucleophilic aromatic substitution. Suitable bases include, for example, n-BuLi, $LiN(Si(CH_3)_3)_2$, and NaH. Carbamate **33** can be synthesized by exposure of **32** to carbonyldiimidazole in DMF, followed by *in situ* silylation of the hydroxymethyl group of the initial product with an appropriate silyl chloride. Desilylation of derivatives of type **31** produces alcohols **17** that can be converted to the targets of the present invention by the processes described herein.

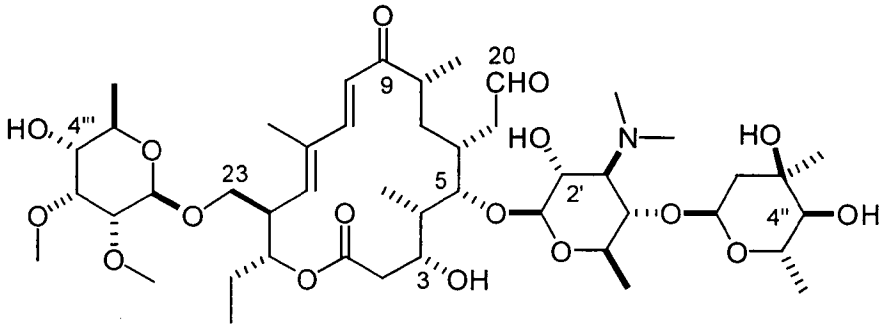
Scheme 3



The 16-membered ring macrolide antibiotics are a diverse class of compounds. Many naturally occurring antibiotics in this class are known in the art and many more have been created by partial synthesis from those natural products. Most of these compounds share in common the feature of having the amino sugar mycaminose at the C-5 position of the macrolide ring. The mycaminose may be present by itself, or more commonly as part of a disaccharide linked through the 4' hydroxy group of the mycaminose. The chemistry demonstrated below involves substitution of the mycaminose sugar, either on the 3' nitrogen atom, or at the adjacent 4' hydroxy group. The examples illustrated below all proceed from the tylosin-derived semisynthetic compound desmycosin or a protected derivative thereof. Nonetheless, it will be clear to those skilled in the art that analogous chemistry can also be applied to the other members of the class of 16-membered macrolides with success.

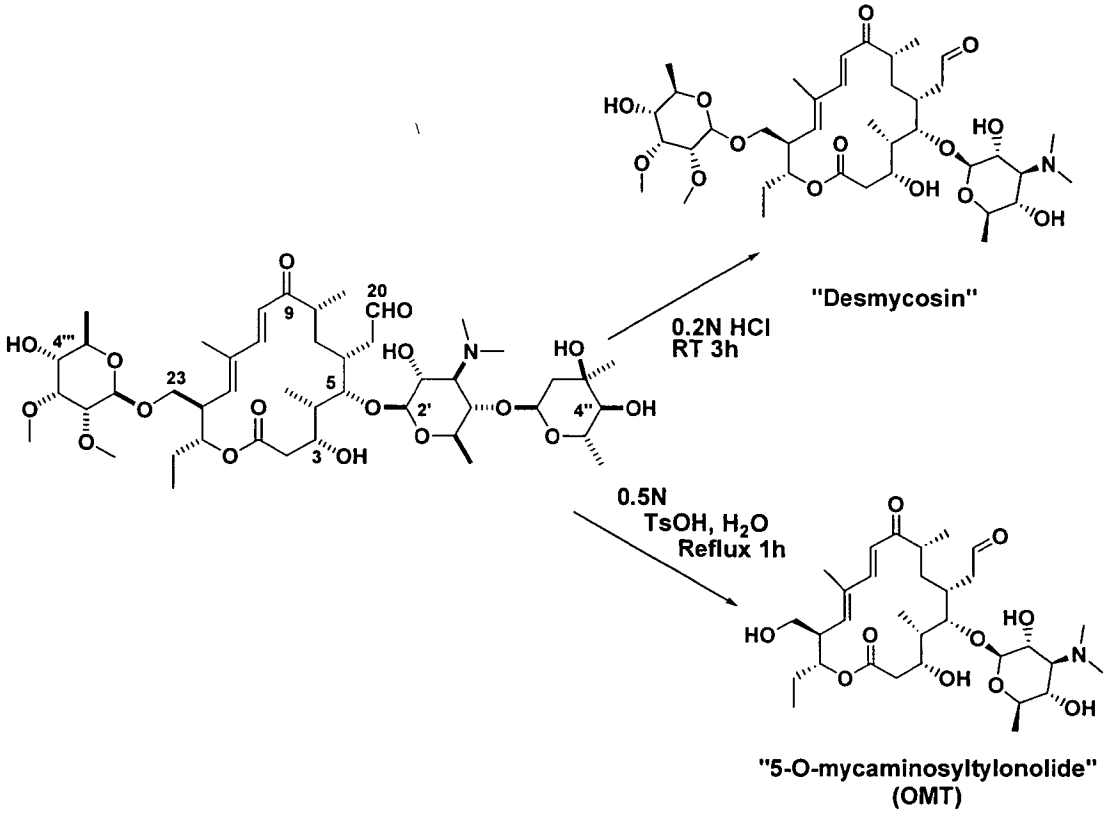
Tylosin comprises four cyclic fragments: three hexose sugars (mycinose, mycaminose, and mycarose) and a macrocylcic lactone (tylonolide). The positions on mycinose ring are denoted by triple prime numbers; those on the mycarose ring by double prime numbers; and the positions on the mycaminose ring by single prime numbers; while positions on the tylonolide ring are indicated by un-prime numbers. In the present invention, substitution takes place at the 3' or 4' position of the mycaminose moiety.

Tylosin



Tylosin can be treated under acidic conditions to selectively cleave the mycarose sugar. The resulting macrolide disaccharide is known as desmycosin. More strenuous acidic conditions additionally lead to the cleavage of the mycinose sugar giving the monosacharide macrolide 5'-O-mycaminosyltylonolide commonly abbreviated OMT (Scheme 4).

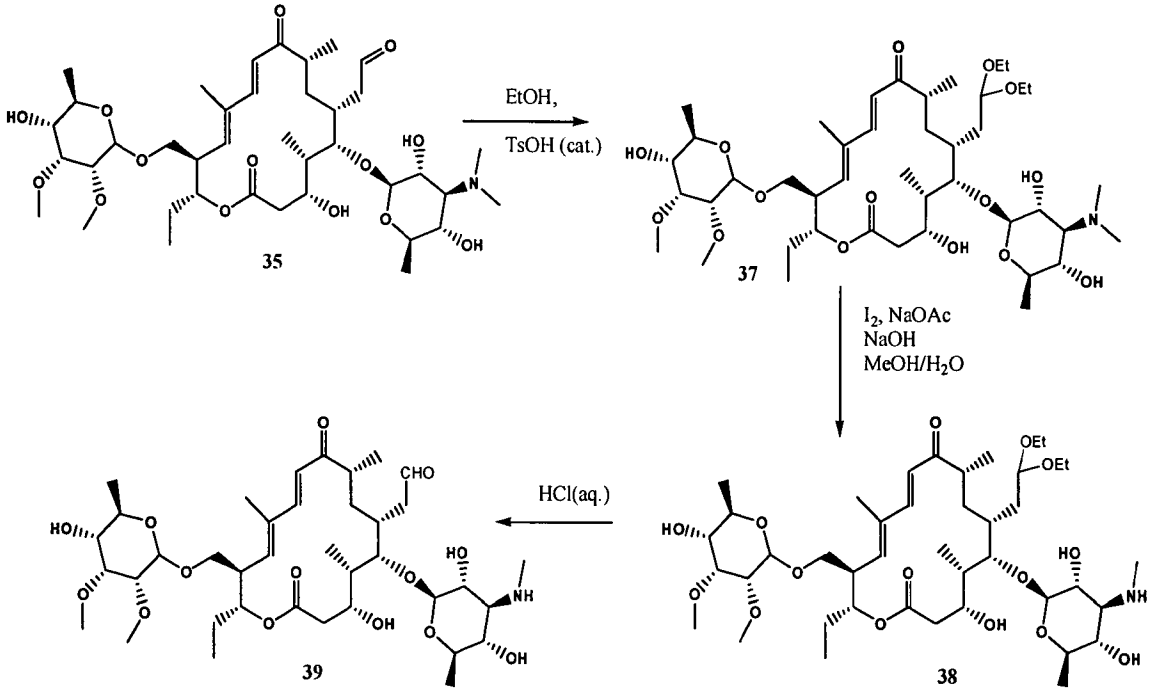
Scheme 4



16-membered macrolides can be mono-N-demethylated, using for example procedures disclosed in US 3,725,385. For instance, desmycosin may be protected as its 20- diethylacetal

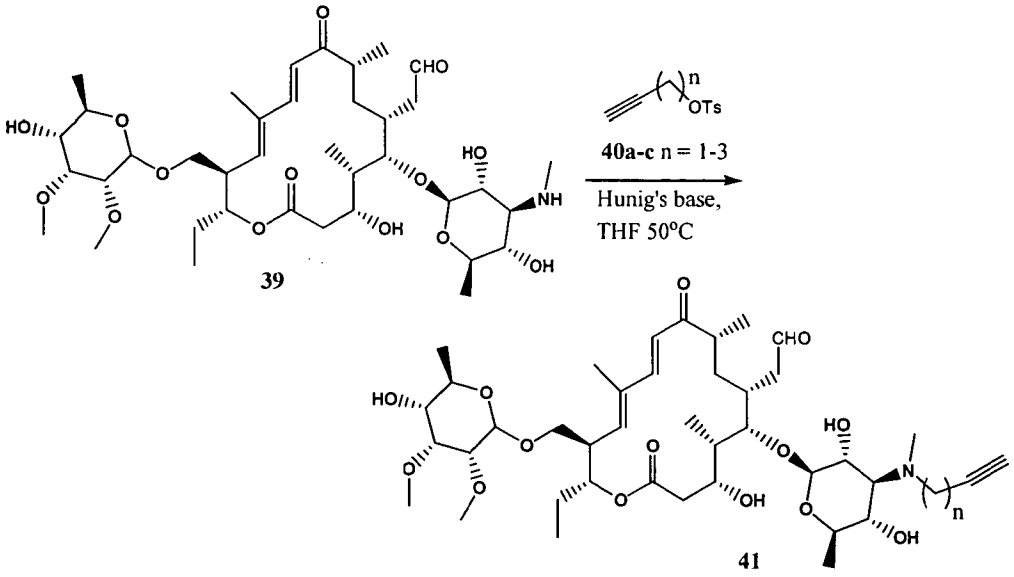
derivative followed by treatment with iodine in the presence of sodium acetate and sodium hydroxide in aqueous methanol to afford the N-desmethyl compound **38**. The diethylacetal protecting group on **38** may then be cleaved under acidic conditions to give aldehyde **39**.

Scheme 5



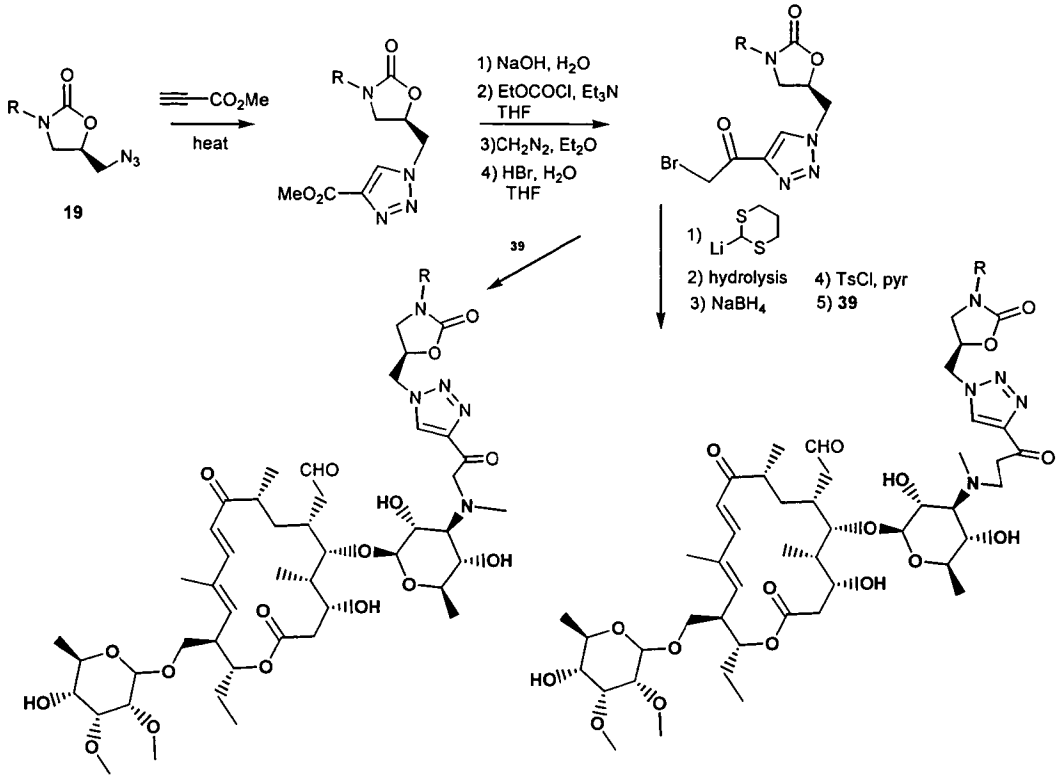
The resulting secondary amines can be alkylated with electrophiles comprised of an alkyne connected by a variable bond or linker to a carbon bearing a leaving group as, for example, a halide or sulfonate group such as **40** to produce alkynes of type **41**. The substituted alkynes **41** thereby obtained can be used in cycloaddition reactions with azides to yield triazole-linked target compounds.

Scheme 6



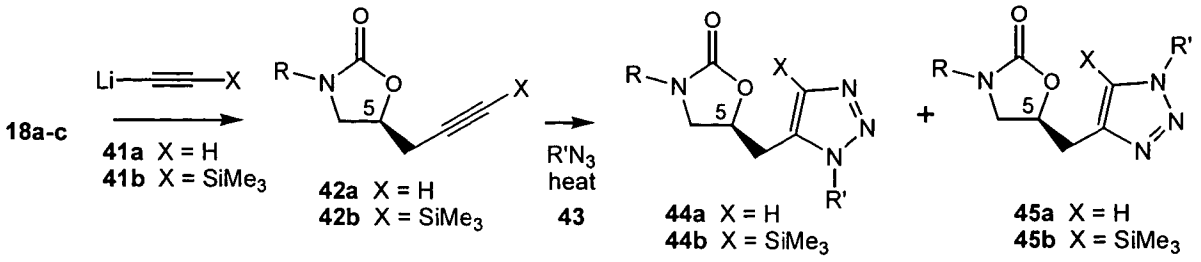
Scheme 7 illustrates the synthesis of compounds of the present invention that contain extra keto groups in the alkyl link between the 5-membered heterocyclic ring and the macrolide moiety. Azides **19** can react with propiolate esters to produce the ester-substituted products. (Mixtures of regioisomeric cycloadducts may form in this reaction. However, only the anti adduct is depicted in Scheme 4b.) Hydrolysis of the ester yields the acid, which can be converted using known chemistry (Ramtohul *et al.*, *J. Org. Chem.*, **2000**, *67*, 3169) to the bromoacetyl triazole. Heating this bromoacetyl derivative with **39** (or a suitably protected version of **39**) can yield products that contain a keto link with one methylene group between the ketone and the macrolide group. The bromoacetyl intermediate can be converted to an alcohol via lithio-dithiane chemistry, subsequent hydrolysis, and reduction. The tosylate (or halide) of this alcohol can be made, and this electrophile can be used to alkylate **39** to give products with two methylene groups between the ketone and the macrolide group.

Scheme 7



Scheme 8 illustrates another method to synthesize regioisomeric triazole-linked derivatives of the present invention. Carbon-linked triazole derivatives of type **44** and **45** can be produced by first displacing a leaving group (for example, a sulfonate or a halide) from electrophiles **18a-c**, with either lithium acetylide **41a** or lithium trimethylsilylacetylide **41b** to produce alkynes **42**. The cycloaddition reaction of alkynes **42** with appropriate azides **43** can yield regioisomeric triazoles **44** and **45**. (Alternative chemical conditions could also be employed to produce compounds **44** and **45**, such as the use of copper(I)iodide instead of heat.)

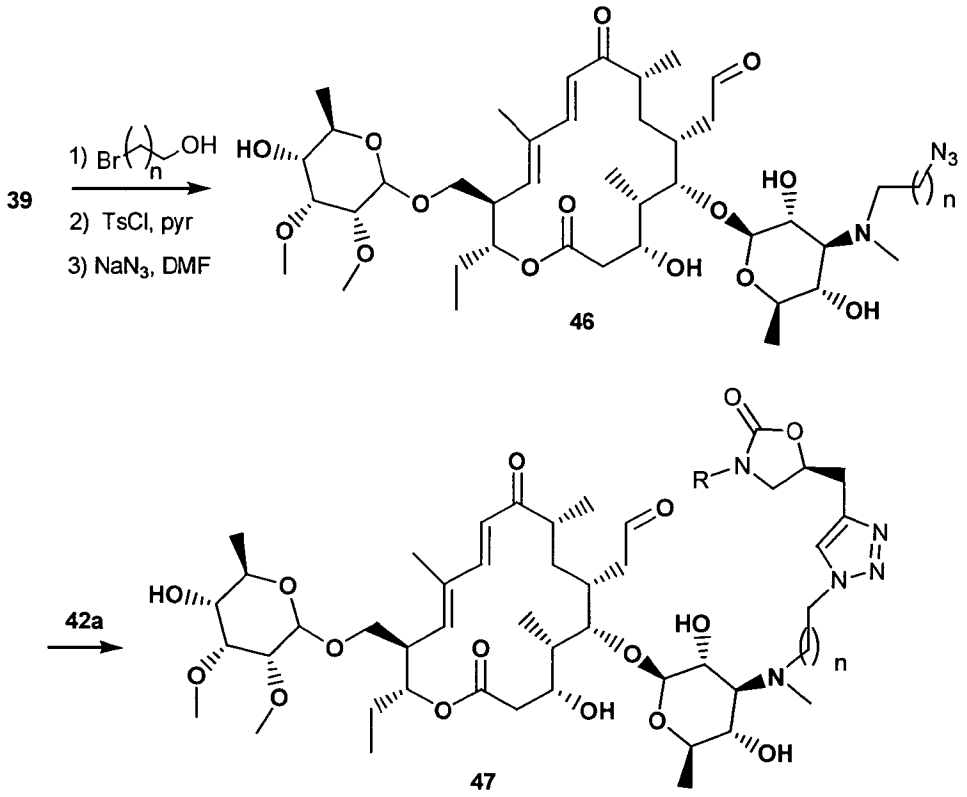
Scheme 8



A specific example of the utility of the chemistry expressed in Scheme 8 is shown in Scheme 9. N-desmethyl desmycosin derivative **39** (or a suitably protected derivative thereof)

can be alkylated with a protected bromoalcohol, and the alcohol functionality of the product converted to a leaving group such as a tosylate. The tosylate can be displaced with sodium azide to yield azide **46**. Cycloadditon of **46** and alkyne **42a** can produce final targets of type **47**. Alternative alkylsulfonates or halides can be used as the starting material for the synthesis of azide **46** (i.e., different leaving groups). Other desmethyl-mycaminose-containing macrolide entities can be used in place of the desmycosin derivative **39** to produce a variety of alternative products.

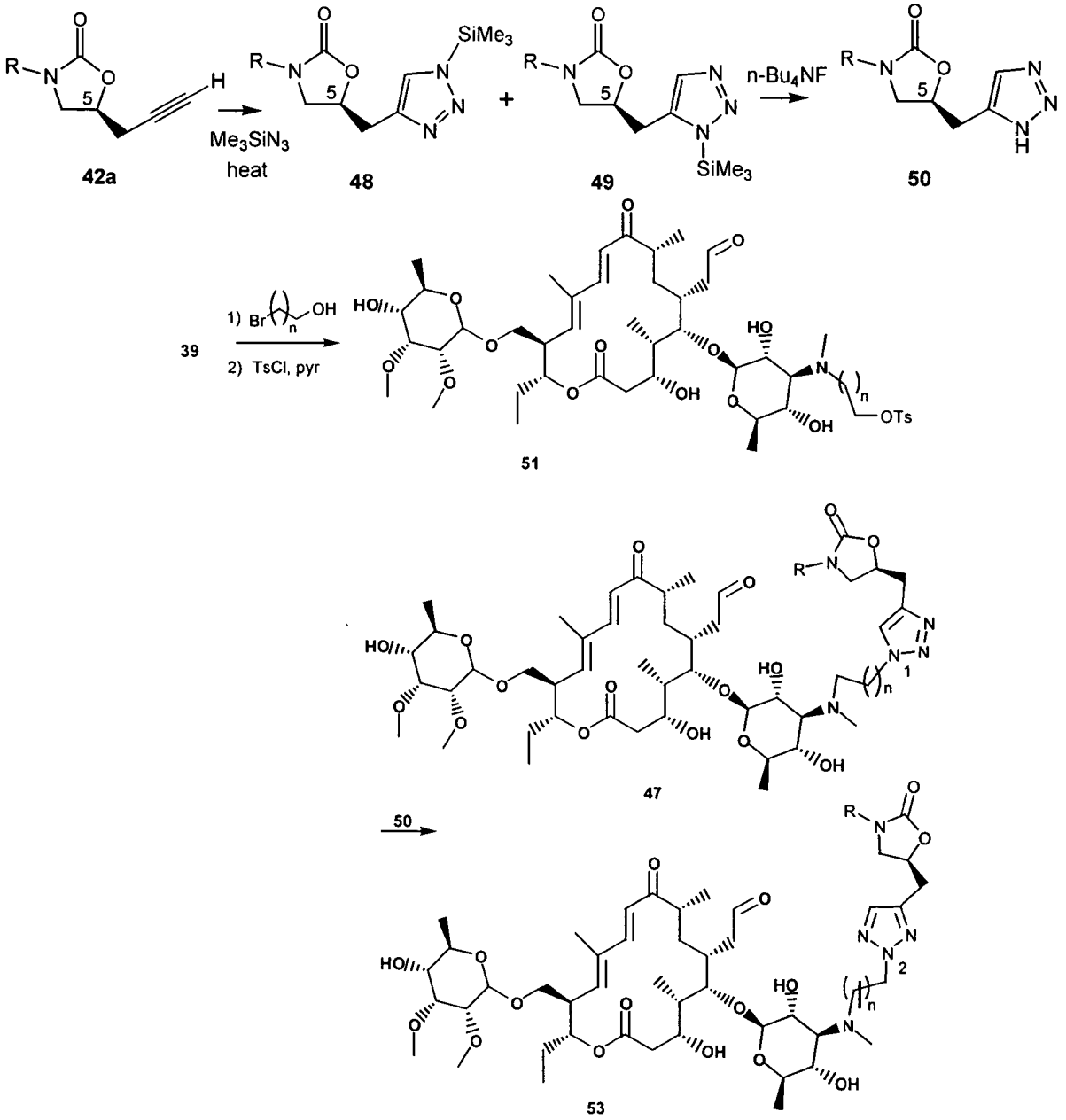
Scheme 9



Another method that can be used to synthesize carbon-linked triazole derivatives of type **47** is illustrated in Scheme 10. Alkyne **42a** can react with trimethylsilylazide (or with sodium azide, ammonium chloride and copper(I)iodide, or other conditions known in the art) to produce two possible regioisomeric products, triazoles **48** and **49**. Either of these (or the mixture) can be desilylated with n-Bu_4NF to produce triazole **50**. Desmethyl desmycosin derivative **39** (or an alternate desmethyl amino macrolide derivative) can be converted to tosylate **51** (or another sulfonate or halide electrophile), and then this electrophile can serve to alkylate triazole **50** to produce either the N-1 substituted triazole **47**, the N-2 substituted triazole **53**, or a mixture of

both. In the event that a mixture is produced, both compounds may be separated from one another. Other macrolides may also be transformed by the chemistry of Scheme 10 to produce other compounds of the present invention.

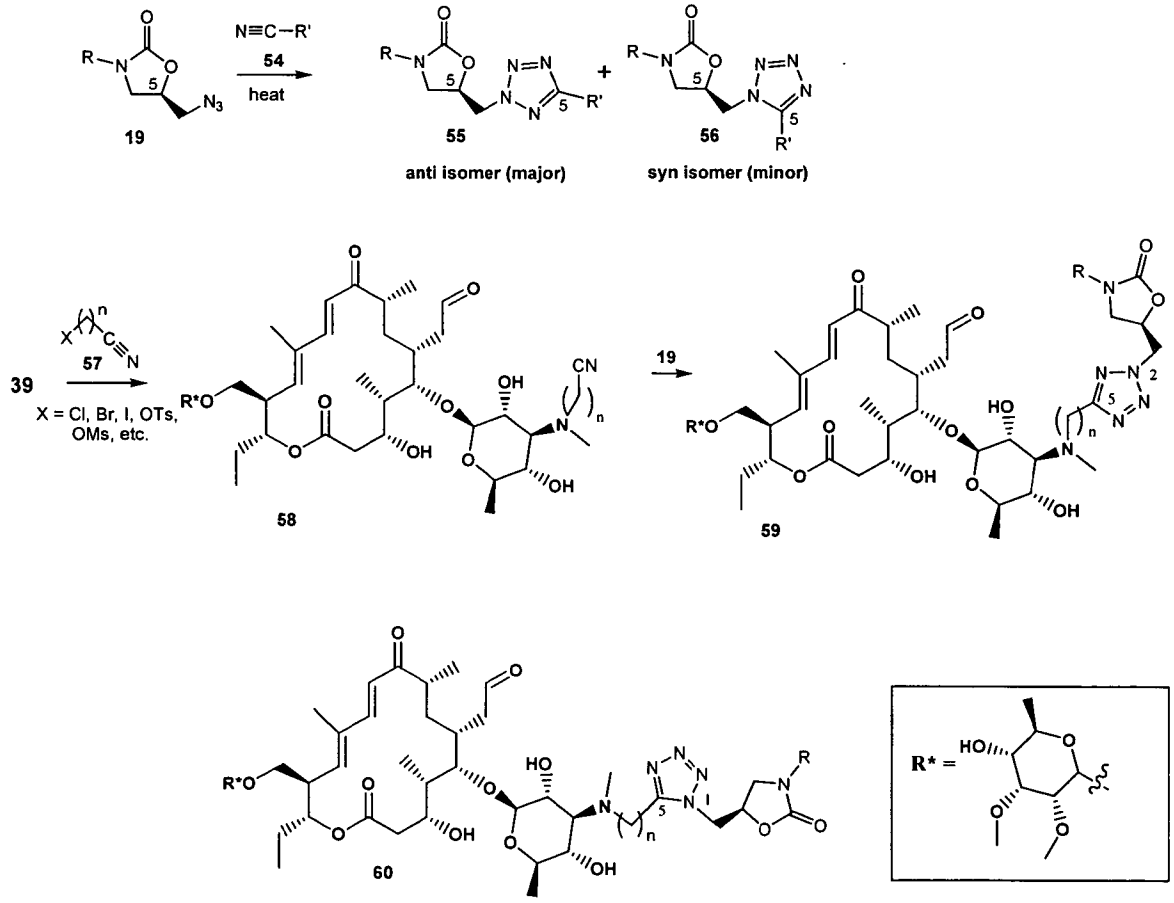
Scheme 10



Scheme 11 illustrates the synthesis of oxazolidinones substituted at C-5 with tetrazolylmethyl derivatives. Azides of type **19** can react with nitriles **54** to produce tetrazoles of type **55** and **56**. In a similar fashion to the chemistry described in Scheme 1, this reaction can

yield regioisomeric cycloadducts, where the anti isomer often predominates. As an example, des-methyl desmycosin **39** can be alkylated with ω-halo or ω-sulfonate nitriles **57** to yield nitriles **58**. These derivatives can react with azides of type **19** to produce target tetrazoles of type **59** and **60**. The R' group of nitriles **54** may contain the macrolide moiety, or suitable substituted alkyl groups containing an alcohol or protected alcohol that could be converted to a leaving group prior to a final alkylation step with a macrolide. Thus, the tetrazoles **55** and **56** could be produced that have as their R' groups alkyl chains bearing a hydroxy group that can be converted into a sulfonate or halide leaving group prior to alkylation with amines similar to **39** to afford products of type **59** and **60**.

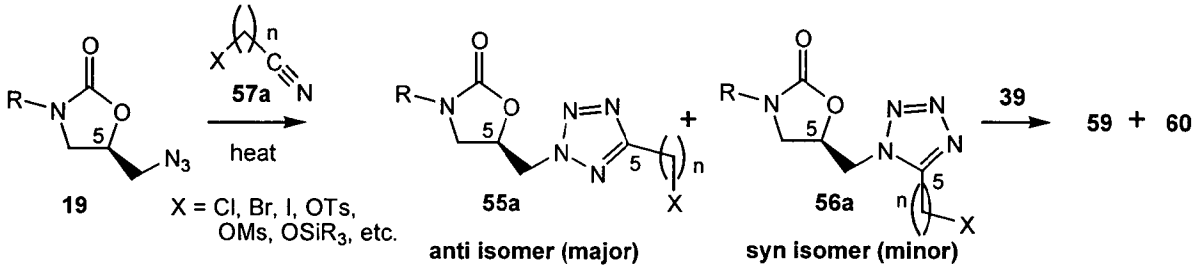
Scheme 11



Scheme 12 depicts another strategy to synthesize tetrazoles of type **59** and **60**. Azides **19** could undergo cycloaddition with functionalized nitriles of type **57a** to afford tetrazole intermediates **55a** and **56a**. If **55a** and **56a** contain an appropriate electrophilic group such as a

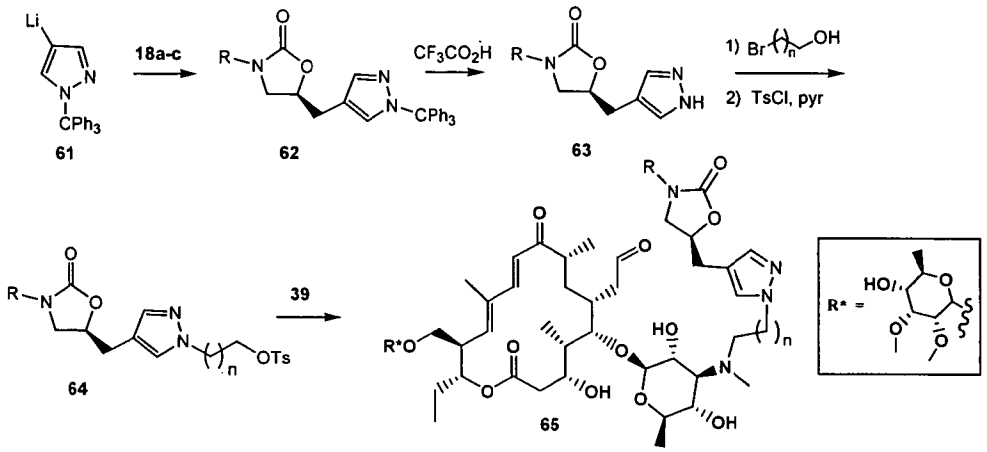
halide or sulfonate, it can react directly with macrolides of type **39** (or a suitably protected derivative thereof) to yield targets of type **59** and **60**. Alternatively, silyloxy-substituted nitriles **57a** could be used during the cycloaddition reaction to afford intermediates of type **55a** and **56a** where X is a silyloxy group. The silylether protecting group could then be removed from **55a** and **56a**, and the resultant alcohol converted to an appropriate electrophile (such as a halide or sulfonate) that would then be suitable for alkylation of macrolides of type **39** to give the desired targets.

Scheme 12



Scheme 13 illustrates one method of synthesizing pyrazole derivatives of the present invention. Known trityl-protected organolithium derivative **61** (Elguero *et al.*, *Synthesis*, **1997**, 563) can be alkylated with electrophiles of type **18a-c** to produce pyrazoles of type **62**. Cleavage of the trityl group can be accomplished using a variety of acidic reagents, for example, trifluoroacetic acid (TFA), to produce pyrazole **63**. Alkylation of **63** with a bromoalcohol of appropriate length, followed by tosylation (or alternate sulfonation or halide formation) can produce electrophiles **64**. Alkylation of **39** with **64** produces targets of type **65**. The lithium anions derived from heterocycles such as **61** may optionally be converted to copper (or other metallic) derivatives to facilitate their displacement reactions with sulfonates and halides. These anions may also be allowed to react with suitably protected macrolides, such as the per-silylated derivative of **51**.

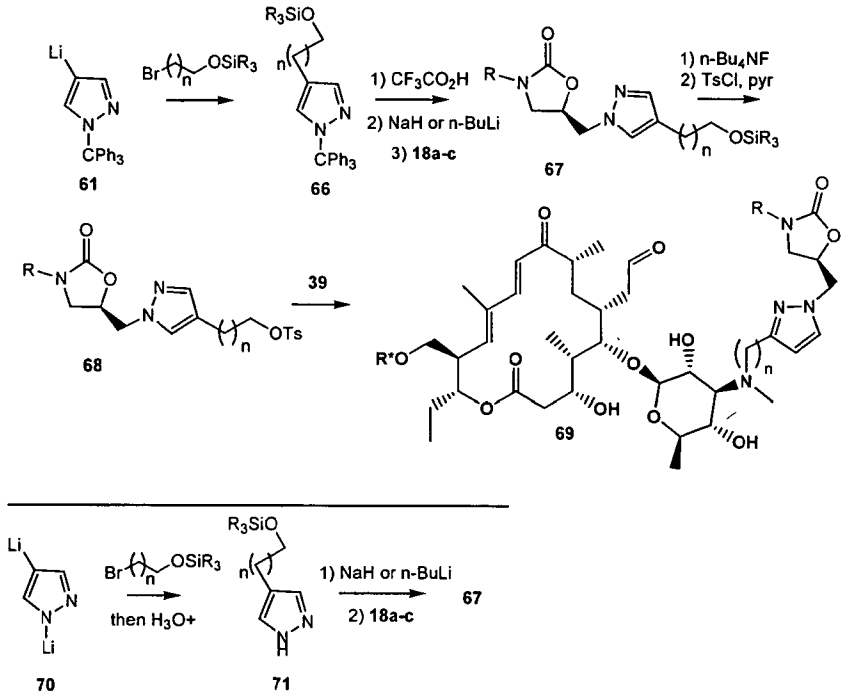
Scheme 13



Scheme 14 depicts another method of synthesizing pyrazoles of the present invention. Anions **61** can be alkylated with a bifunctional linker of variable length, such as an alkyl halide containing a silyloxy derivative. Alternatively, an α, ω dihaloalkyl derivative or a mixed halo-sulfonate derivative can be used as the alkylating agent. The resulting substituted pyrazoles **66** can be converted to the free pyrazoles by TFA cleavage of the triphenylmethyl protecting group. The free pyrazoles can undergo direct alkylation with electrophiles **18a-c** in a suitable solvent, for example, dimethylformamide, or can be first converted via deprotonation with a suitable base, for example, sodium hydride or n-butyllithium, to the corresponding anion, if a more reactive nucleophile is required. The resultant pyrazole derivatives **67** can be desilylated and converted to tosylates **68** (if a sulfonate strategy is employed), which can serve as electrophiles for subsequent reaction with macrolide desmethyl saccharides, for example, **39,** to produce the resultant target **69**.

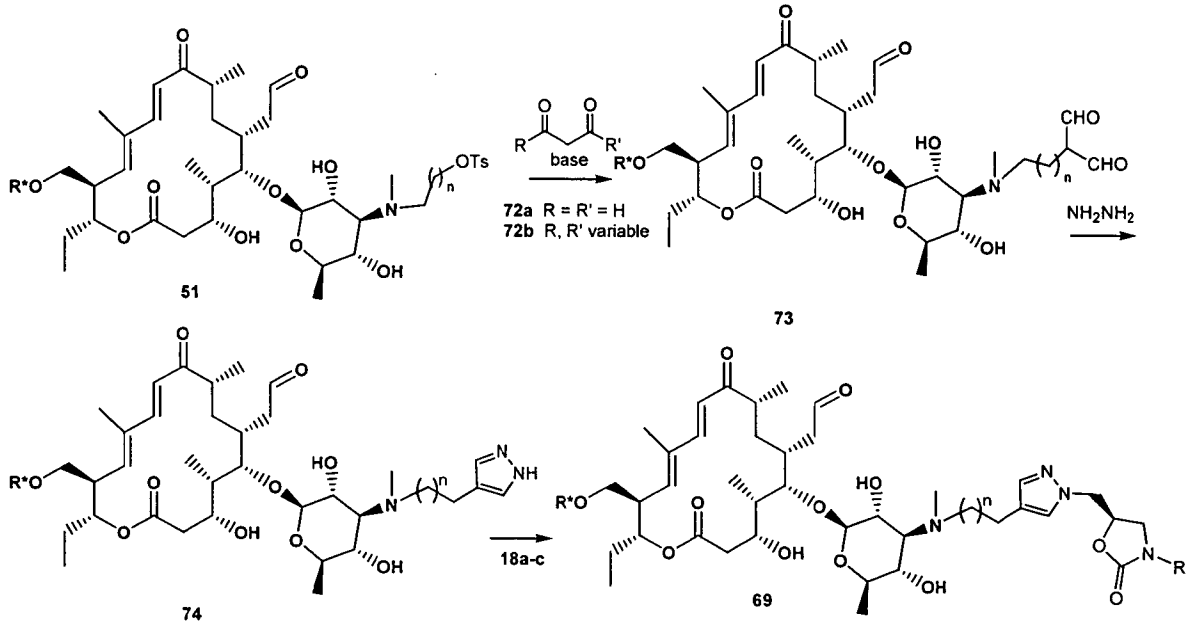
Another approach to intermediates of type **67** can start with alkylation of the known dianion **70** (Hahn *et al., J. Het. Chem.*, **1991**, *28*: 1189) with an appropriate bifunctional linker to produce compounds related to pyrazole **71**, which can subsequently be alkylated (with or without prior deprotonation) with electrophiles **18a-c** to produce intermediates **67**. The n=1 derivatives in this series can be synthesized by trapment of compound **61** with DMF to produce the corresponding aldehyde, and then reduction to the alcohol. Alternatively, methoxymethyl (MOM) chloride or bromide can serve as the alkylating reagent for **61**, and hydrolysis of the trityl and MOM groups of the product would yield 4-hydroxymethyl-1,2-pyrazole. The dianion of this pyrazole can be alkylated on nitrogen to produce an alcohol that serves as the precursor for an n=1 tosylate (or other leaving group).

Scheme 14



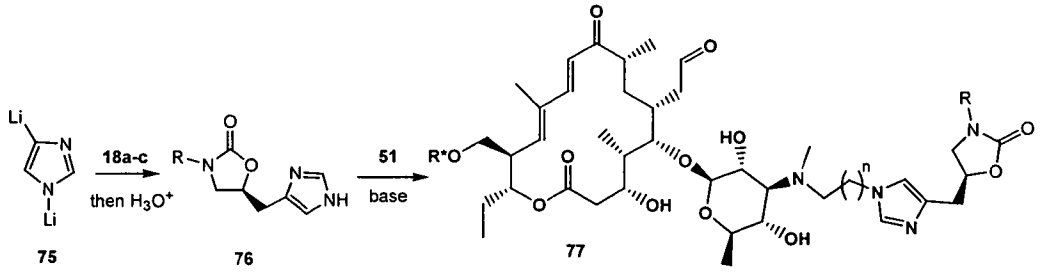
Scheme 15 shows an alternate approach for synthesizing pyrazole derivatives of type **69**. Alkylation of the anion of a β-dicarbonyl system with appropriate electrophiles similar to tosylate **51** can yield (in the specific example of β-dicarbonyl derivative **72a**) products of type **73**. Treatment of these intermediates with hydrazine can produce pyrazoles of type **74**. Direct alkylation of **74** with electrophiles **18a-c** can proceed to produce targets **69**. Alternatively, the hydroxyl residues of **74** (and other sensitive functional groups of other macrolide derivatives such as intermediates **39** and **51**) can be protected with suitable protecting groups (such as those highlighted in Greene, T.W. and Wuts, P.G.M. *supra*), and the hydrogen atom on the nitrogen atom of the pyrazole derivative deprotonated with a suitable base, for example, sodium hydride or n-butyllithium. The resulting anion can then be alkylated with electrophiles **18a-c**, and the resulting product deprotected to produce target **69**. The use of protecting groups well known to those skilled in the art for the macrolide portions of these intermediates may be required for many of the subsequent reactions shown in the schemes below that involve heteroaryl anion alkylations.

Scheme 15



Scheme 16 exemplifies a synthesis of imidazoles of the present invention. The known dianion **75** (Katritzky *et al.*, *J. Chem. Soc. Perkin Trans.*, **1989**, *1*, 1139) can react with electrophiles **18a-c** to produce, after protic work-up, imidazoles of type **76**. Direct alkylation of **76** by heating with electrophiles related to **51** in an appropriate organic solvent can yield 1,4-disubstituted imidazoles **77**. Alternatively, the imidazole anion formed via deprotonation of the imidazole hydrogen atom of **76** with a suitable base and then alkylation with **51** can also produce **77**.

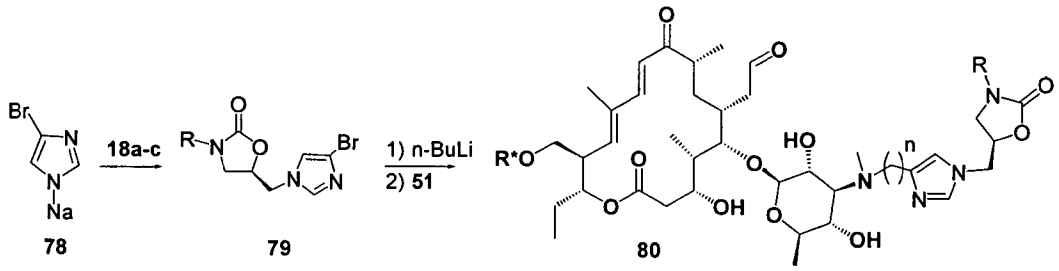
Scheme 16



Scheme 17 illustrates another synthesis of imidazoles of the present invention. 4-Bromoimidazole can be deprotonated using, for example, sodium hydride or lithium diisopropylamide, or another suitable organic base, to give anion **78** (or the corresponding lithio

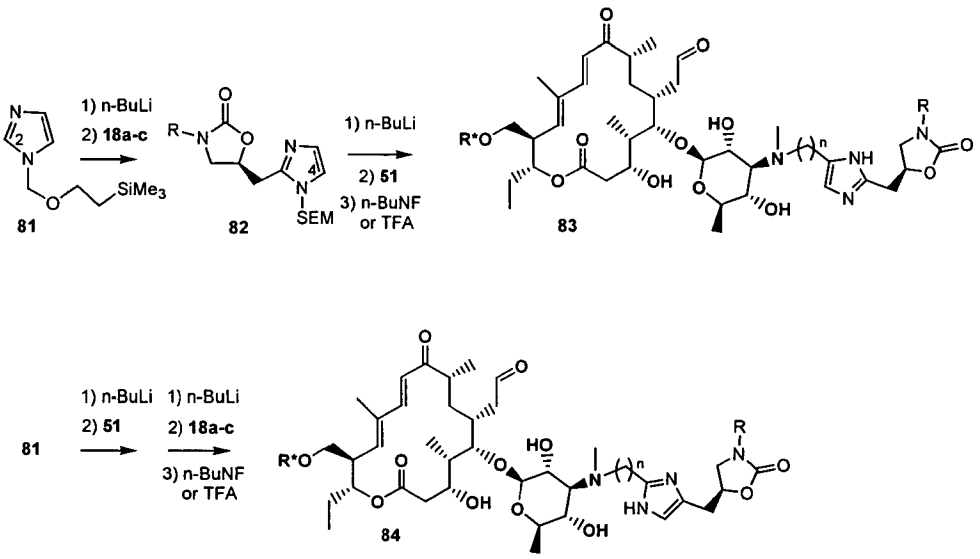
derivative). Alkylation of **78** with **18a-c** can yield bromoimidazole **79** which can then be subjected to metal-halogen exchange and alkylated with **51** (or a suitably protected derivative of **51**) to produce isomeric 1,4-disubstituted imidazoles **80**.

Scheme 17



Scheme 18 depicts chemistry suitable for the synthesis of other target imidazole derivatives. The silylethoxymethyl (SEM) protected imidazole can be lithiated at C-2 (Shapiro *et al.*, *Heterocycles*, **1995**, *41*, 215) and can react with electrophiles **18a-c** to produce imidazole intermediates **82**. Lithiation of imidazole intermediates **82** at C-4 of the imidazole, followed by alkylation with electrophiles of type **51** (or a suitably protected version such as the per-silylated derivative), and then deprotection of the SEM can produce imidazoles **83**.

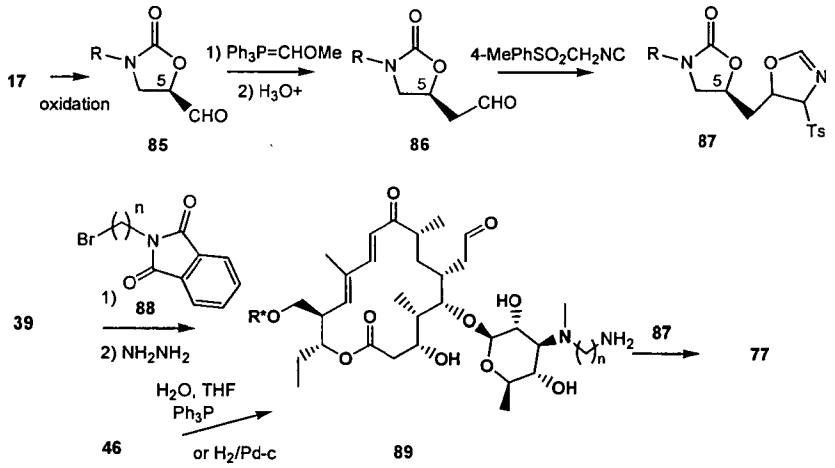
Scheme 18



Scheme 19 shows how tosylmethyl isocyanide can be used to make imidazoles of the present invention (Vanelle *et al.*, *Eur. J. Med. Chem.*, **2000**, *35*, 157; Horne *et al.*, *Heterocycles*,

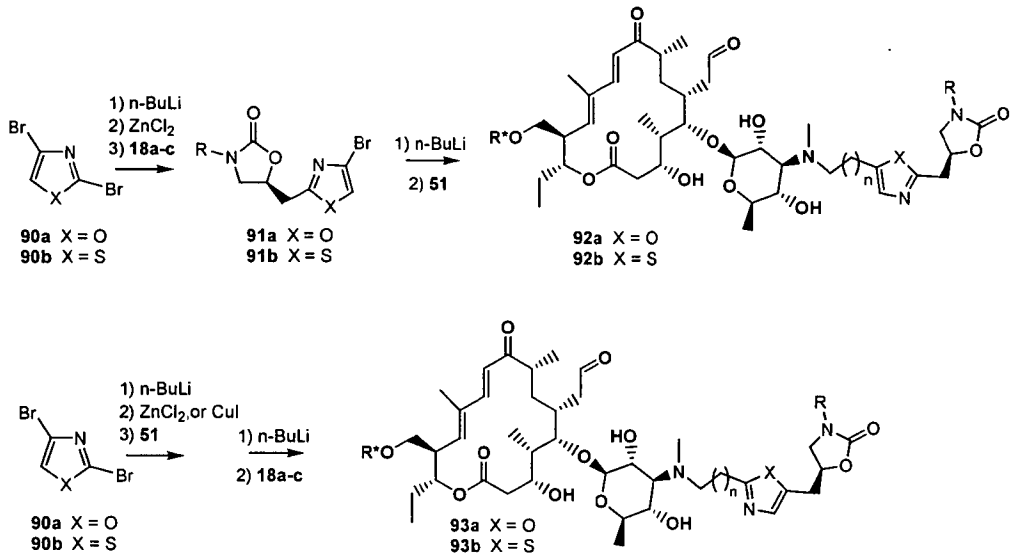
1994, *39*, 139). Alcohols **17** can be oxidized to produce aldehydes **85** using an appropriate agent such as the Dess-Martin periodinane or oxalyl chloride/dimethylsulfoxide/triethylamine (Swern oxidation). A variety of chromium complexes can also be used for this oxidation, including, for example, pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), chromium trioxide, and tetrapropylammonium perruthenate. Wittig homologation of **85** can provide aldehyde **86**, which can then be converted by tosylmethyl isocyanide to produce intermediate **87**. The reaction of **87** with **89** (formed via alkylation of amines **39** with bromoalkyl phthalimides **88** (followed by hydrazine cleavage) or reduction of azides **46**) can produce imidazole **77**.

Scheme 19



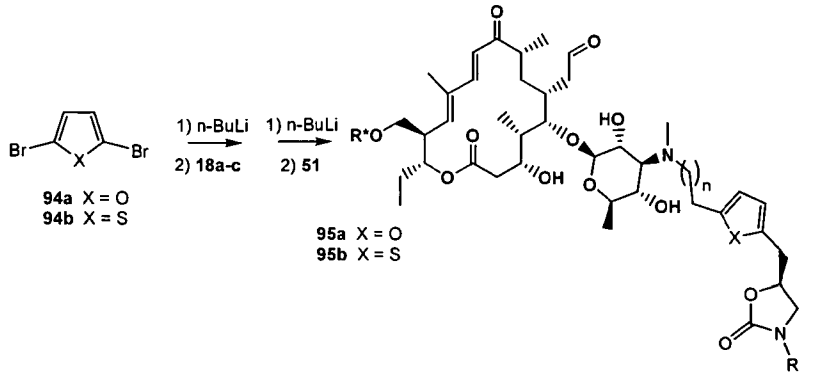
Scheme 20 delineates how 1,3 thiazole and 1,3 oxazole derivatives of the present invention can be synthesized. Known dibromo thiazoles and oxazoles **90a** and **90b** can be selectively metallated at C-2 and alkylated with electrophiles **18a-c** to produce intermediates **91a** and **91b** (Pinkerton *et al.*, *J. Het. Chem.*, **1972**, , 67). Transmetallation with zinc chloride can be employed in the case of the oxazole anion, if the anion displays any tendency to ring open prior to its reaction with certain electrophiles. The bromo azoles **91** can be metallated to form the corresponding anion that can undergo alkylation with sulfonates **51** (or the related halides) to produce the final targets **92**. Reordering of the sequence of electrophiles in this process permits access to the isomeric thiazoles and oxazoles **93**.

Scheme 20



Scheme 21 shows the synthesis of 2,5 disubstituted furan and thiophene derivatives of the present invention. Commercially available dibromofuran **94a** and dibromothiophene **94b** can be monolithiated (Cherioux *et al.*, *Advanced Functional Materials*, **2001**, *11*: 305) and alkylated with electrophiles **18a-c**. The monobromo intermediates obtained from this reaction can be lithiated again and then alkylated with electrophiles of type **51** (or a protected version of **51**) to produce the final targets **95**.

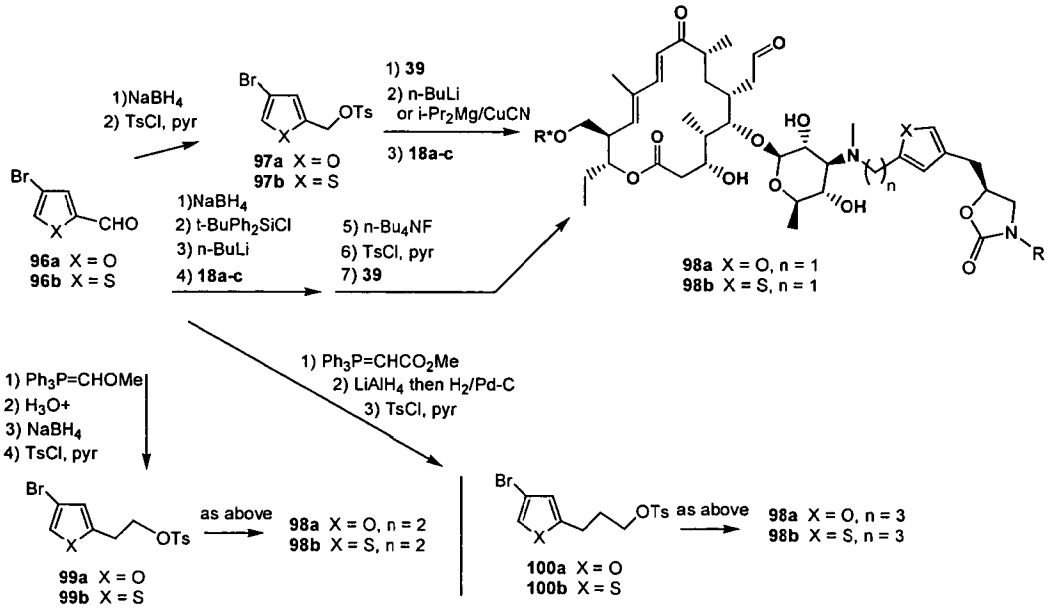
Scheme 21



Scheme 22 depicts the synthesis of 2,4 disubstituted furan and thiophene derivatives of the present invention. Commercially available furan aldehyde **96a**, and the known thiophene aldehyde **96b**, can be reduced to the corresponding alcohols and the resulting alcohols converted

to a leaving group such as tosylates **97**. Alternate sulfonates and halides can be synthesized and used in this fashion. The tosylates **97** can alkylate alcohol **39** (or a protected version thereof), and the heteroaryl bromide can be converted to a suitable organometallic agent (by reagents such as n-BuLi, or i-Pr_2Mg/CuCN). This intermediate organometallic agent can be alkylated with electrophiles **18a-c** to produce targets of type **98**, where n=1. As the scheme shows, a reordering of steps can be employed involving reduction, silylation, lithiation, and then initial alkylation with **18a-c**. Desilylation of the alkylation product, followed by tosylation of the alcohol, provides an intermediate that can then be alkylated with alcohol **39** to produce targets **98**. Simple homologation protocols, using the reagents depicted in Scheme 22 or others known to those skilled in the art, can convert the aldehydes **96** to longer chain tosylates such as **99** and **100**. The use of these tosylates in the alkylation with **39**, and subsequent metal-halogen exchange and alkylation with **18a-c**, can yield compounds of type **98** where n=2 or 3. Longer chain tosylates can also be produced using chemistries similar to that depicted in Scheme 22. In addition, other bifunctional linkers can be used to produce compounds of type **98**.

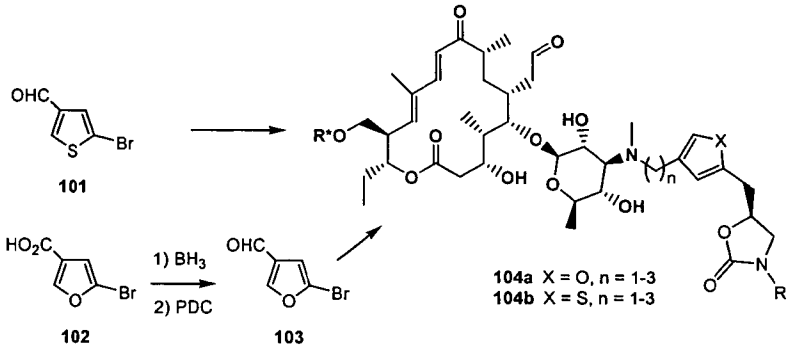
Scheme 22



Chemistries similar to that employed above in Scheme 22 can convert known thiophene aldehyde **101** (Eras *et al.*, *J. Het. Chem.*, **1984**, *21*, 215) to produce products of type **104** (Scheme 23). The known acid **102** (Wang *et al.*, *Tetrahedron*, **1996**, *52*, 12137) can be converted to aldehyde **103** by reduction with, for example, borane or lithium aluminum hydride,

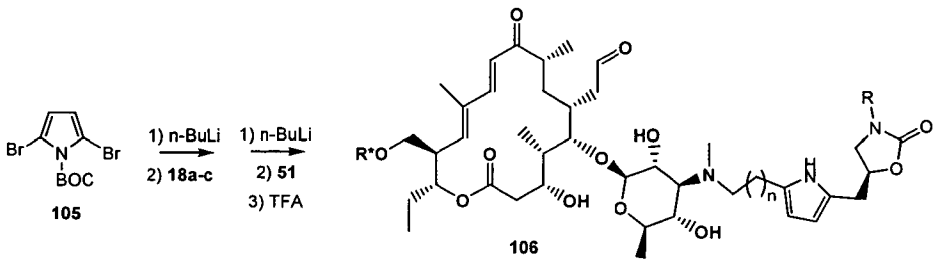
followed by oxidation of the resultant hydroxymethyl intermediate with, for example, PDC, PCC, or another suitable reagent. Aldehyde **103** can then be converted to produce compounds of type **104**.

Scheme 23



Scheme 24 illustrates the synthesis of 2,5 disubstituted pyrroles of the present invention. The BOC-protected dibromopyrrole **105** can be lithiated and alkylated sequentially (Chen *et al.*, *Tetr. Lett.*, **1987**, *28*: 6025; Chen *et al.*, *Org. Synth.*, **1992**, *70*, 151; and Martina *et al.*, *Synthesis*, **1991**, 613), and allowed to react with electrophiles **18a-c** and **51** (or a suitably protected analogue of **51**) to produce, after final BOC deprotection with TFA, disubstituted pyrroles of type **106**.

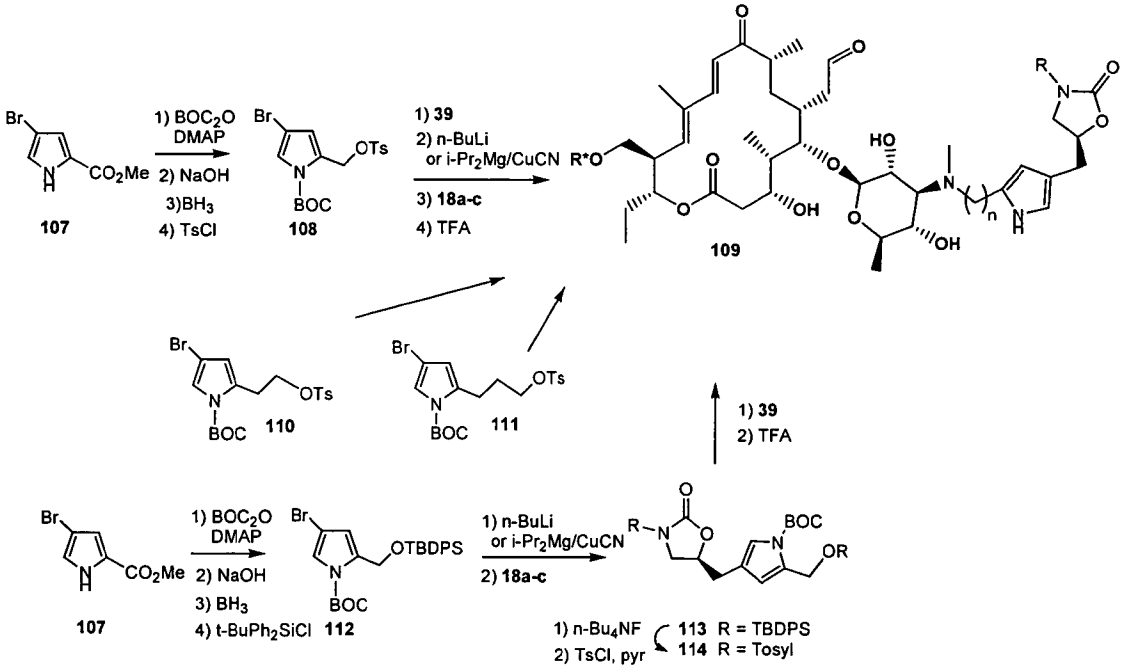
Scheme 24



Scheme 25 shows the synthesis of 2,4 disubstituted pyrroles of the present invention. Commercially available pyrrole ester **107** can be protected with a suitable protecting group, for example, the BOC group, and the ester function hydrolyzed to the corresponding acid. The resulting acid can then be reduced to the alcohol using, for example, borane to yield an alcohol that can be converted to tosylate **108**. Alcohol **39** (or a suitably protected version of **39**, formed for example by silylation of the other hydroxyl groups with bis-trimethylsilylacetamide or another silylating reagent) can be alkylated with tosylate **108** to produce an intermediate

bromopyrrole. The bromopyrrole can then be converted to an organometallic reagent that can then react with electrophiles **18a-c**. The resulting product can then be deprotected with TFA to produce pyrroles **109**. The alcohol formed after borane reduction of the acid derived from **107** can then be homologated to tosylates **110** and **111** by chemistries similar to that shown below in Scheme 27. The use of these tosylates in the alkylation strategy can produce target pyrroles of type **109** where n=2 or 3.

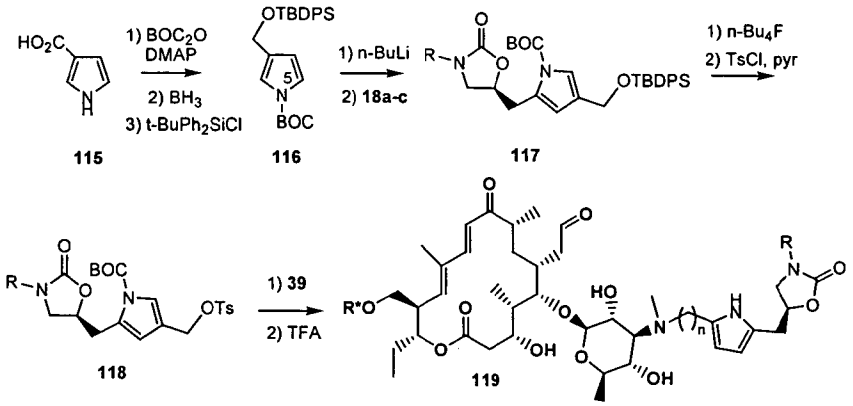
Scheme 25



An alternative approach is to protect the alcohol functions prior to tosylation, and perform the alkylation of the organometallic derived from the halopyrrole with **18a-c** first. For example, silyloxy derivative **112** can be produced from **107**, and the organometallic derivative derived from it alkylated with **18a-c** to yield silyl ethers **113**. Subsequent desilylation and conversion to tosylates **114** provides an electrophile that can be used in the alkylation reaction with **39**. A final BOC cleavage can then give pyrroles **109**. The alcohol precursor of **112** can be homologated, using chemistries similar to that shown below in Scheme 27 and other schemes) to other alkanols that can be tosylated for further reactions with alcohol **39** (or related macrolides). Furthermore, the alcohol derived from silyl cleavage of **113** can serve as the starting material for this type of homologation effort to produce the alkyl tosylates (or halides) required for making targets **109** where n is variable.

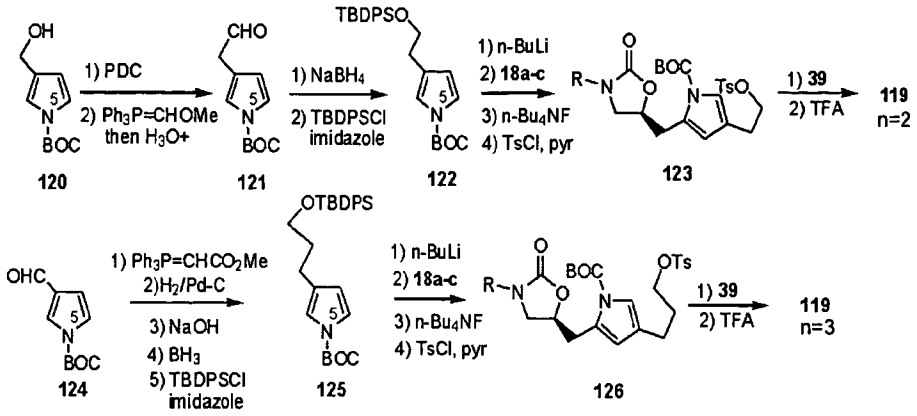
Scheme 26 shows the synthesis of isomeric 2,4 disubstituted pyrroles of the present invention. Commercially available pyrrole acid **115** can be protected as the BOC derivative, and the acid function reduced to an alcohol, which can then be protected to produce the silyl ether **116**. Deprotonation of **116** with n-butyllithium can occur at the 5 position of the pyrrole ring, and this anion (or that derived from transmetallation with an appropriate metal) can be alkylated with electrophiles **18a-c** to produce pyrrole **117**. Desilylation of **117**, followed by tosylation, alkylation with **39**, and TFA deprotection of the BOC group can yield pyrroles **119**.

Scheme 26



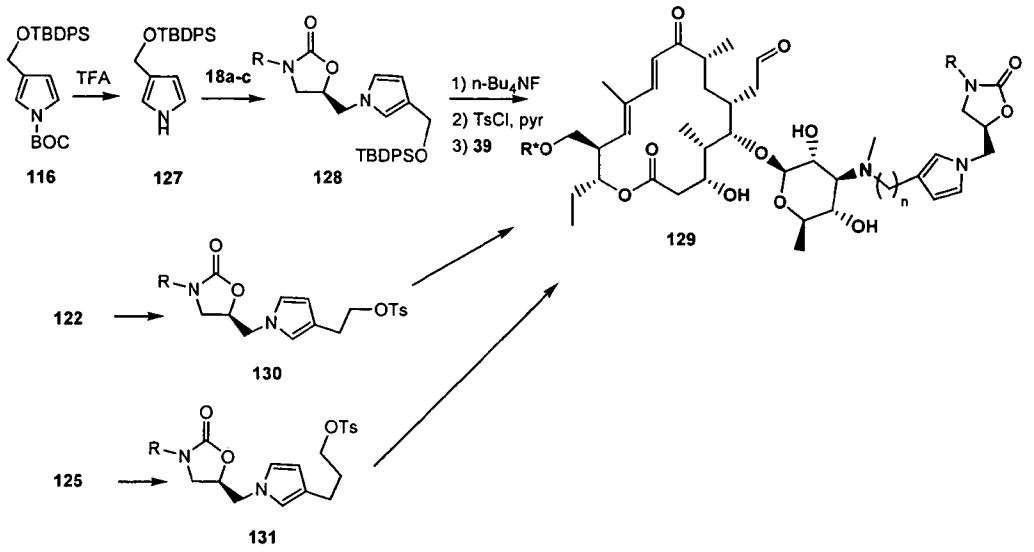
Scheme 27 illustrates the synthesis of longer chain tosylates of type **123** and **126** used to alkylate amines of type **39** to produce pyrroles **119**. The alcohol **120** derived from protection of **115** followed by borane reduction can be oxidized to aldehyde **124**. The Wittig reaction of aldehyde **124** with methoxymethyl triphenylphosphorane is followed by an acid hydrolysis step to produce the homologated aldehyde **121**. Reduction and silyl protection can yield **122**, which can then be deprotonated, alkylated, and then converted to tosylate **123**. Aldehyde **124** can undergo a Wittig reaction with carbomethoxymethyl triphenylphosphorane. The Wittig product then is reduced to an alkanol that can then be silylated to produce **125**. Conversion of **125** to pyrroles **119** can then occur using the same chemistry employed to provide **119** from **122**.

Scheme 27



Scheme 28 shows the synthesis of 1,3 disubstituted pyrroles of the present invention. The BOC group of **116** can be cleaved to produce free pyrrole **127**. Alkylation of **127** (in a suitable organic solvent such as DMF) with **18a-c** can produce intermediate **128**. The dianion of 3-hydroxymethylpyrrole can also be suitable for alkylation with **18a-c** to produce the free hydroxy derivative of silyl ether **128**. Conversion of the siloxy group to the corresponding tosylate, followed by alkylation with amines of type **39** can generate the target N-substituted pyrroles **129** (where n=1). In a similar fashion, the BOC pyrroles **122** and **125** can be converted to the tosylates **130** and **131**. These tosylates can be used to produce pyrroles of type **129** (where n=2 or 3). Longer chain alkyl tosylates (and halides) can also be produced that can undergo this chemistry to produce pyrroles **129** where n is > 3.

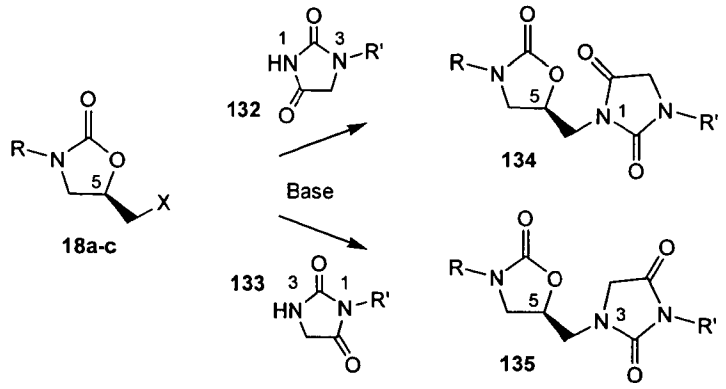
Scheme 28



Scheme 29 illustrates the use of hydantoin-like groups as the 5-membered heterocyclic linker between the G groups and the R_1 moieties of the present invention. Electrophiles of type **18a-c** can alkylate anions derived from hydantoins to produce compounds of the present invention. For example, 3-substituted hydantoins of type **132** can be purchased and treated with an appropriate base to generate the corresponding imide anion. The resulting anions can be alkylated with electrophiles similar (but not limited) to intermediates **18a-c** to produce hydantoin derivatives **134**. Alternatively, 1-substituted hydantoins of type **133** can be purchased or prepared, and treated with base and electrophile to yield isomeric hydantoin derivatives **135**. Such hydantoins can also have, for example, at optional locations, thiocarbonyl functionalities in place of the illustrated carbonyl groups. Such compounds can be prepared by treatment of the oxy-hydantoins with Lawesson's reagent, elemental sulfur, phosphorus pentasulfide, and other reagents commonly used in the art to perform this transformation.

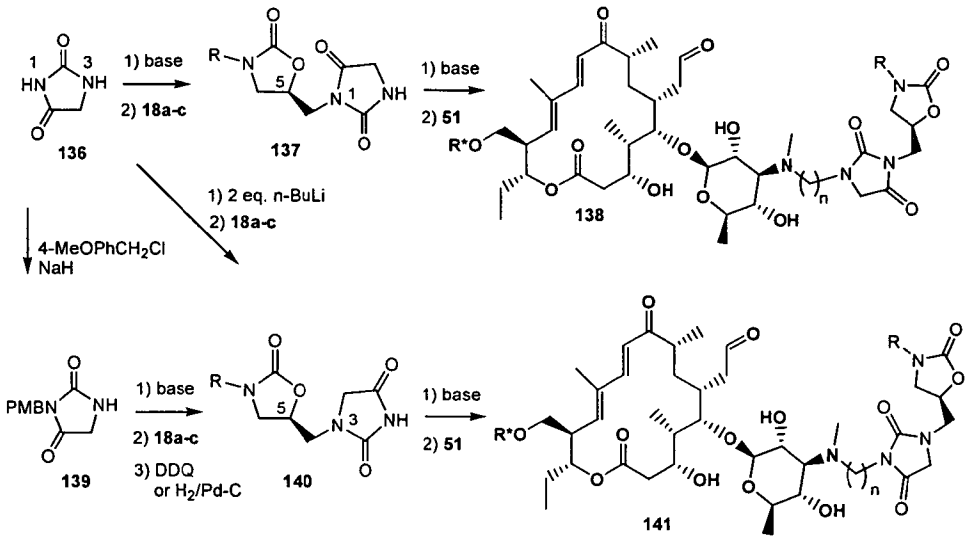
Alternatively, such thiohydantoins can be synthesized selectively by sequential synthetic steps known in the art. The R' group of **132** and **133** may represent a protecting group function, for example, benzyl, alkoxybenzyl, benzyloxycarbonyl, t-butoxycarbonyl, that is compatible with the alkylation step. Such a protecting group can subsequently be removed from products **134** and **135**, yielding products where the R' group is a hydrogen atom. These intermediates can be used to produce various target molecules by their treatment with base and then subsequent exposure to appropriate electrophiles.

Scheme 29



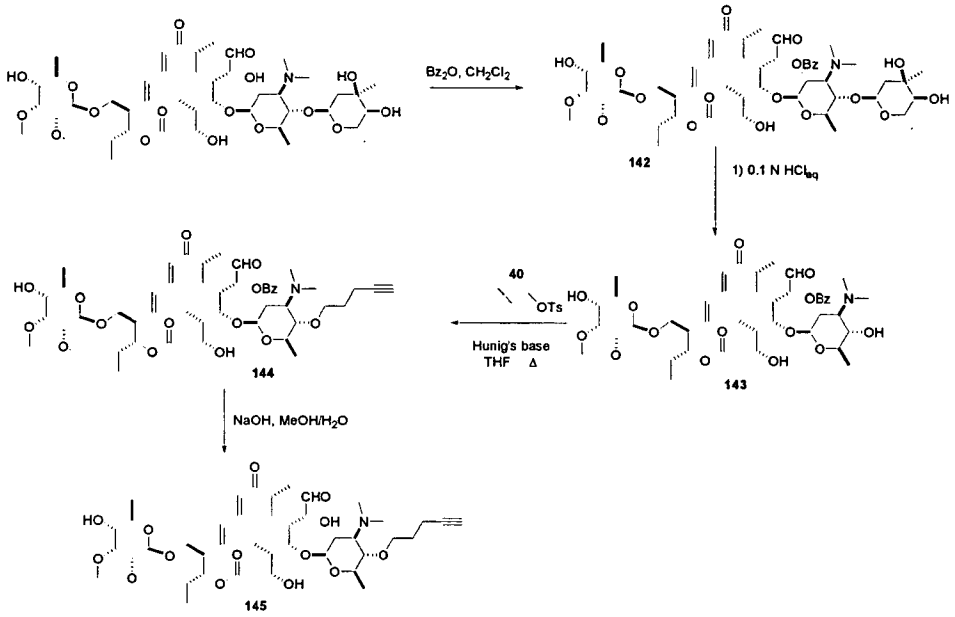
A more specific example of the synthesis of hydantoin derivatives of the present invention is depicted in Scheme 30. Hydantoin **136** can be treated with a mild organic base, for example, sodium hydride, potassium tertiary-butoxide, cesium, sodium, or potassium carbonate, to produce the N-1 substituted intermediate **137**. Deprotonation of **137** with a base, for example, sodium hydride, n-butyllithium, lithium bis-trimethylsilylamide, or lithium diisopropylamide, followed by alkylation with **51** (or a suitably protected derivative of **51**) can yield hydantoin targets of type **138**. The isomeric hydantoin derivatives of type **141** can be synthesized from **136** by initial p-methoxybenzyl (PMB) protection of the N-1 position, followed by alkylation at N-3 with **18a-c**, and subsequent deprotection of the PMB group with either 2,3-dichloro-3,4-dicyano-benzoquinone (DDQ) or hydrogenation will yield hydantoin intermediates **140**. Subsequent alkylation of **140** with **51** can give compounds **141**. Another route to produce intermediates **140** is by formation of the dianion of hydantoin **136**. One equivalent of a weak base can deprotonate the N-1 position of **136**. The addition of another equivalent of a strong base, for example, n-butyllithium, to the initial anion can deprotonate it again, this time at N-3. Alkylation can occur at the more reactive position (N-3) to again produce hydantoins **140**.

Scheme 30



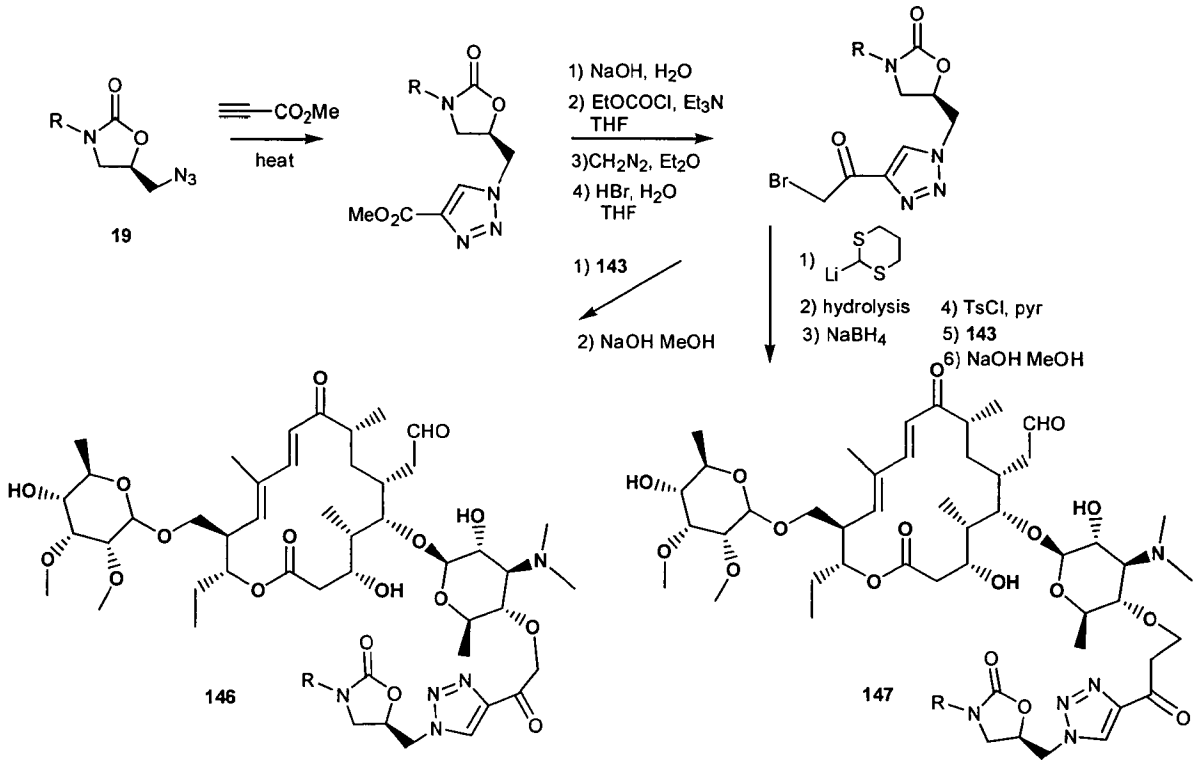
In addition to the above-described compounds, the present invention includes compounds in which the 16-membered macrolide moiety is linked to an oxazolidinone or oxazolidinone fragment by connection through a heterocyclic linker attached to the 4' hydroxy group of the mycaminose sugar. As shown in scheme 31 below, this position may be selectively alkylated with alkynes such as **40**. To accomplish this, the reactive hydroxyl group at the 2' of mycaminose ring is first protected with an acid-stable protecting group prior to hydrolysis of the mycarose moiety from the 4' position (such as, for instance, benzoyl, t-butyldiphenylsilyl, p-nitrobenzylcarbonate, etc.). The free 4' hydroxyl group thus produced is then able to be selectively alkylated due to the reaction-enhancing influence of the adjacent dimethyl amino group at C-3'. Alkylation may then be followed by removal of the protecting group at the 2' position, either before or after further synthetic manipulations as required.

Scheme 31

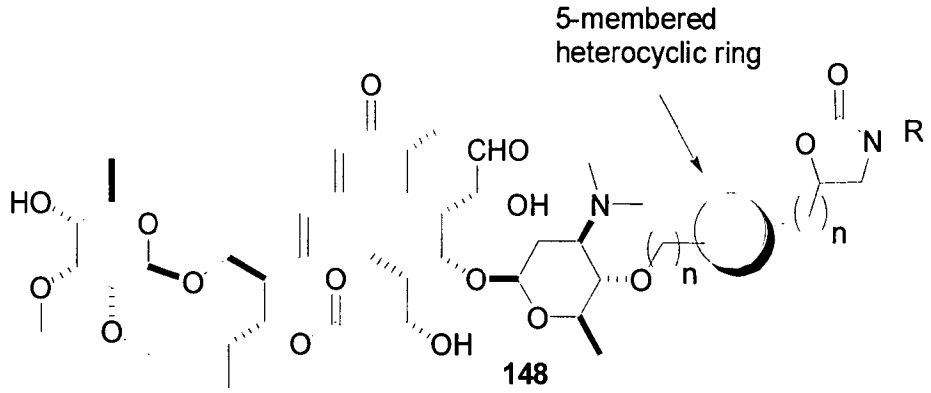


The substituted alkynes **145** thereby obtained can be used in cycloaddition reactions with azides to yield triazole-linked target compounds. Scheme 32 illustrates the synthesis of compounds of the present invention that contain extra keto groups in the alkyl link between the 5-membered heterocyclic ring and the macrolide moiety. Azides **19** can react with propiolate esters to produce the ester-substituted products. (Mixtures of regioisomeric cycloadducts may form in this reaction, however, only the anti adduct is depicted in Scheme 32.) Hydrolysis of the ester yields the acid, which can be converted using known chemistry (Ramtohul *et al.*, *J. Org. Chem.*, **2000**, *67*, 3169) to the bromoacetyl triazole. Heating this bromoacetyl derivative with **143** (or a suitably protected version of **143**) can yield products that contain a keto link with one methylene group between the ketone and the macrolide group. The bromoacetyl intermediate can be converted via lithio-dithiane chemistry, subsequent hydrolysis, and reduction to an alcohol. The tosylate (or halide) of this alcohol can be made, and this electrophile can be used to alkylate **143** to give products with two methylene groups between the ketone and the macrolide group.

Scheme 32



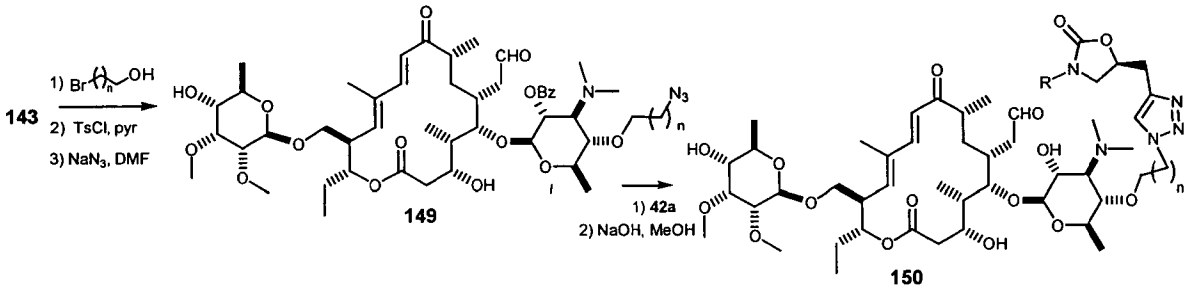
Numerous of the examples presented in schemes 1 to 30 above can also be adapted using a reactive alcohol of type **143** in place of the amine moiety shown in each example to afford numerous compounds of the general structure **148** shown below.



Scheme 9 above illustrates another method to synthesize regioisomeric triazole-linked derivatives of the present invention. A specific example of the utility of the chemistry expressed in Scheme 9 above is shown in Scheme 33. Alcohol **143** (or a suitably protected derivative thereof) can be alkylated with a protected bromoalcohol, and the alcohol function of the product converted to a leaving group such as a tosylate. The tosylate can be displaced with sodium azide

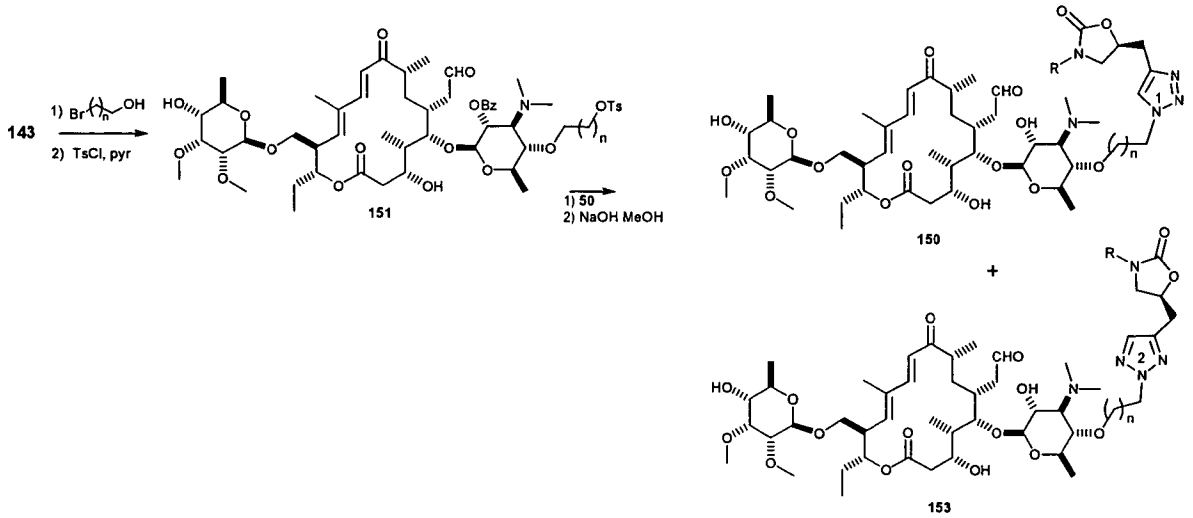
to yield azide **149**. Cycloadditon of **149** and alkyne **42a** followed by removal of the benzoate protecting group can produce final targets of type **150**. Alternative alkylsulfonates or halides can be used as the starting material for the synthesis of azide **149** (i.e., different leaving groups). Other mycaminose-containing macrolide entities can be used in place of the desmycosin derivative **143** to produce a variety of alternative products.

Scheme 33



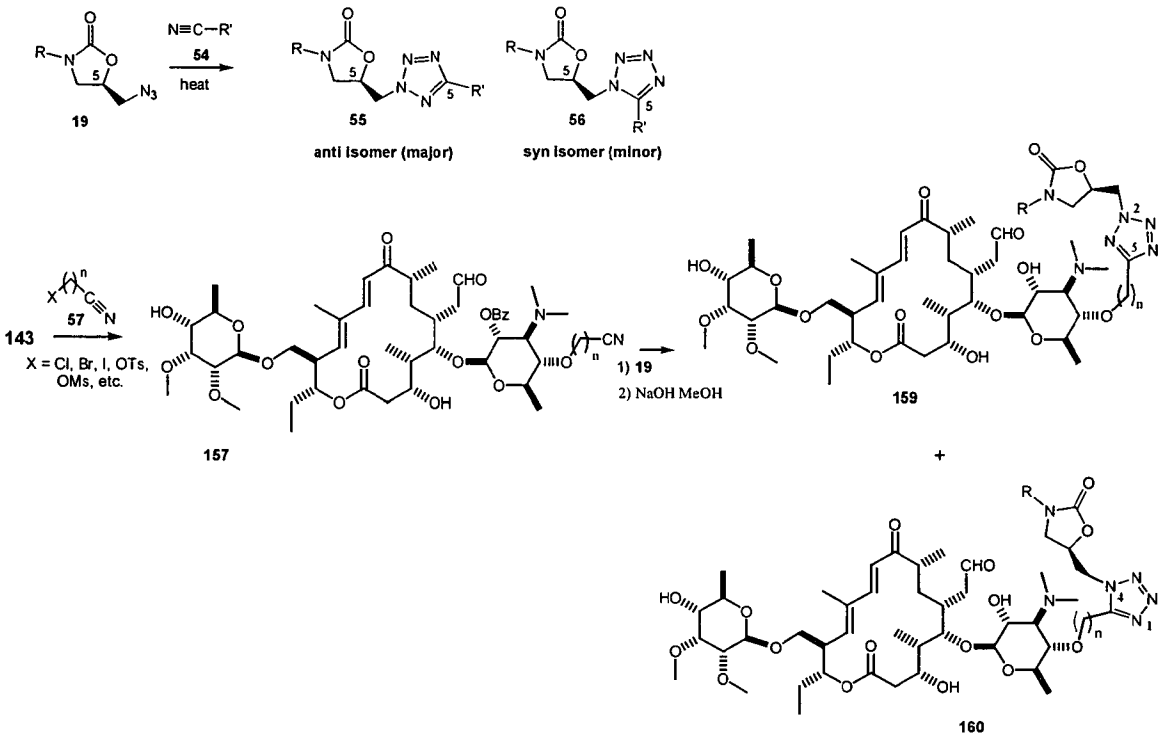
Another method that can be used to synthesize regioisomeric triazole derivatives of type **150** and **153** is illustrated in Scheme 34. Desmycosin derivative **143** (or an alternate mycamionose-containing macrolide derivative) can be converted to tosylate **151** (or another sulfonate or halide electrophile), and then the electrophile can serve to alkylate triazole **50** to produce either the N-1 substituted triazole **150**, or the N-2 substituted triazole **153**, or a mixture of both. In the event that a mixture is produced, both compounds may be separated from one another. Other macrolides may also be transformed by the chemistry of Scheme 34 to produce other compounds of interest.

Scheme 34



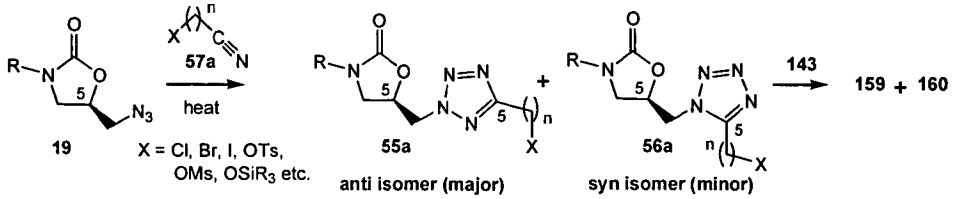
Scheme 35 illustrates the synthesis of oxazolidinones substituted at C-5 with tetrazolylmethyl derivatives. Azides of type **19** can react with nitriles **54** to produce tetrazoles of type **55** and **56**. In a similar fashion to the chemistry described in Scheme 1, this reaction can yield regioisomeric cycloadducts, where the anti isomer often predominates. As an example, desmycosin derivative **143** can be alkylated with ω-halo or ω-sulfonate nitriles to yield nitriles **158**. These derivatives can react with azides of type **19** to produce target tetrazoles of type **159** and **160**. The R' group of nitriles **54** may contain the macrolide moiety, suitable substituted alkyl groups containing an alcohol, or protected alcohol that could be converted to a leaving group prior to a final alkylation step with a macrolide. Thus, the tetrazoles **55** and **56** could be produced that have as their R' groups alkyl chains bearing a hydroxy group that can be converted into a sulfonate or halide leaving group prior to alkylation with alcohols similar to **143** to afford products of type **159** and **160**.

Scheme 35



Scheme 36 depicts another strategy to synthesize tetrazoles of type **159** and **160**. If **55a** and **56a** contain an appropriate electrophilic group such as a halide or sulfonate, they can react directly with macrolides of type **143** (or a suitably protected derivative thereof) to yield targets of type **159** and **160**. Alternatively, silyloxy-substituted nitriles **57a** could be used during the cycloaddition reaction to afford intermediates of type **55a** and **56a**, where X is a silyloxy group. The silylether protecting group could then be removed from **55a** and **56a**, and the resultant alcohol converted to an appropriate electrophile (such as a halide or sulfonate) that would then be suitable for alkylation of macrolides of type **143** to give the desired targets.

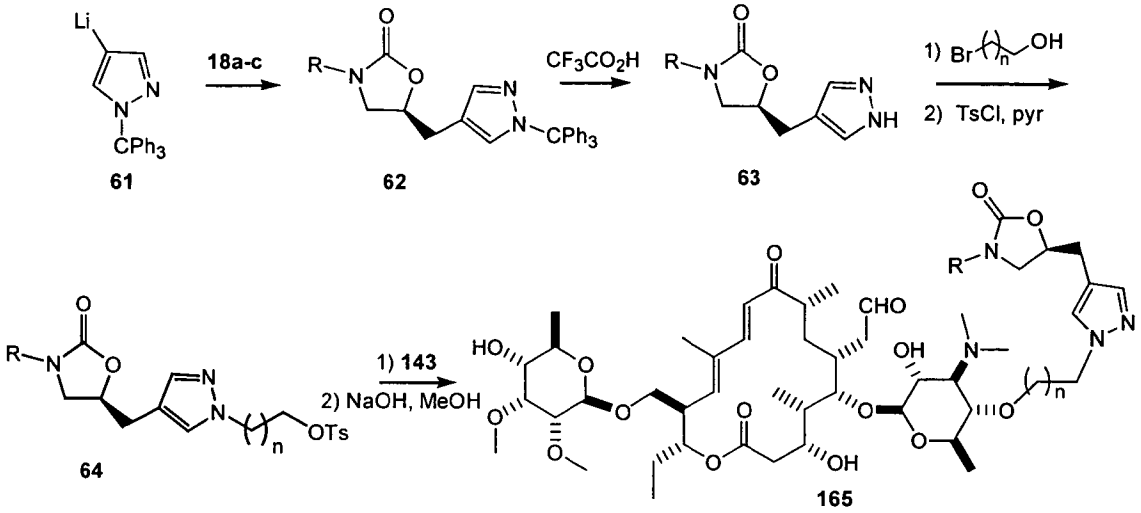
Scheme 36



Scheme 37 illustrates one method of synthesizing pyrazole derivatives of the present invention. Alkylation of **143** with **64** produces targets of type **165**. The lithium anions derived

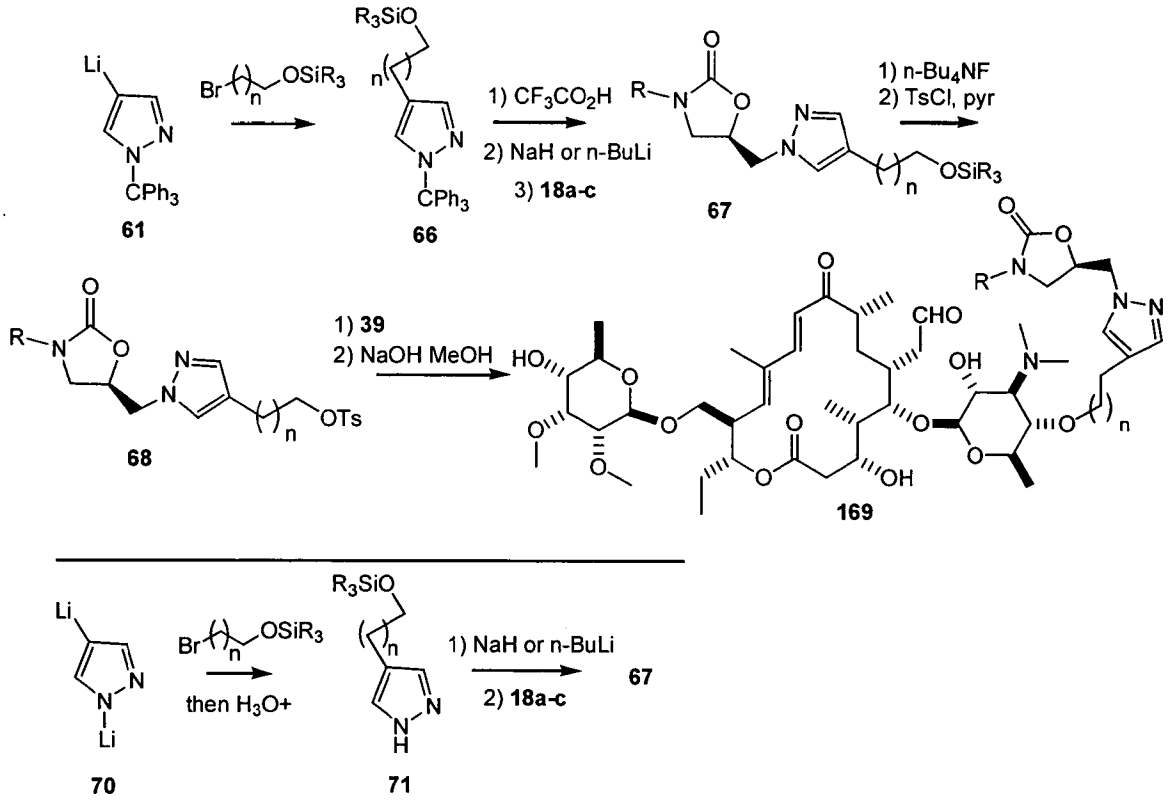
from heterocycles such as **61** may optionally be converted to copper (or other metallic) derivatives to facilitate their displacement reactions with sulfonates and halides. These anions may also be allowed to react with suitably protected macrolides, such as the per-silylated derivative of **151**.

Scheme 37



Scheme 38 depicts another method of synthesizing pyrazoles of the present invention. The pyrazole derivatives **67** can be desilylated and converted to tosylates **68** (if a sulfonate strategy is employed), which can serve as electrophiles for subsequent reaction with macrolide alcohols, for example, **143,** to produce the resultant target **169**.

Scheme 38

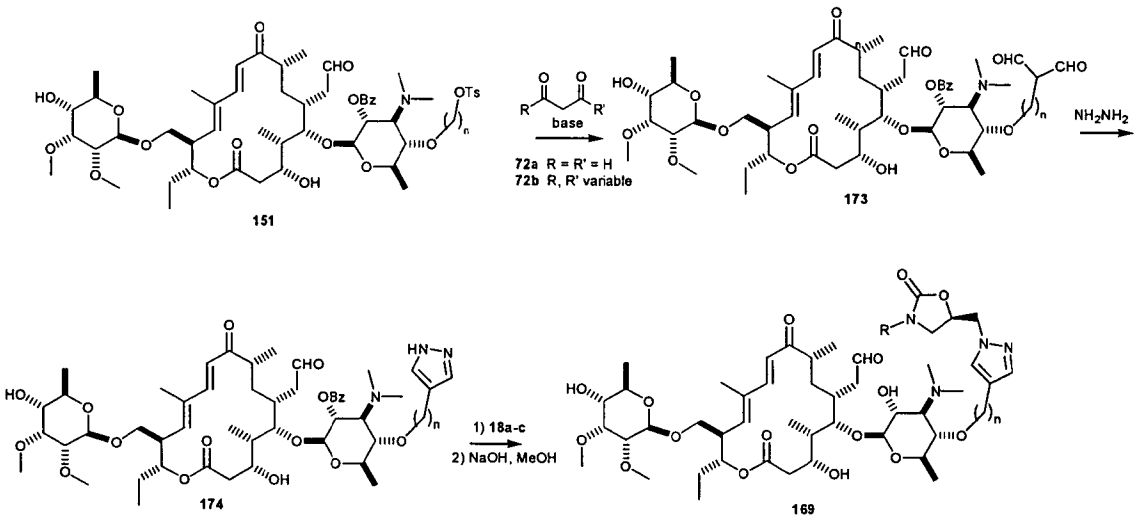


Another approach to intermediates of type **67** can start with alkylation of the known dianion **70** (Hahn *et al.*, *J. Het. Chem.*, **1991**, *28*, 1189) with an appropriate bifunctional linker to produce compounds related to pyrazole **71**, which can subsequently be alkylated (with or without prior deprotonation) with electrophiles **18a-c** to produce intermediates **67**. The n=1 derivatives in this series can be synthesized by trapment of compound **61** with DMF to produce the corresponding aldehyde, and then reduction to the alcohol. Alternatively, methoxymethyl (MOM) chloride or bromide can serve as the alkylating reagent for **61**, and hydrolysis of the trityl and MOM groups of the product would yield 4-hydroxymethyl-1,2-pyrazole. The dianion of this pyrazole can be alkylated on nitrogen to produce an alcohol that serves as the precursor for an n=1 tosylate (or other leaving group).

Scheme 39 shows an alternate approach for synthesizing pyrazole derivatives of type **169**. Alkylation of the anion of a β-dicarbonyl system with appropriate electrophiles similar to tosylate **151** can yield (in the specific example of β-dicarbonyl derivative **72a**) products of type **173**. Treatment of these intermediates with hydrazine can produce pyrazoles of type **174**. Direct alkylation of **174** with electrophiles **18a-c** can proceed to produce targets **169**. Alternatively, the

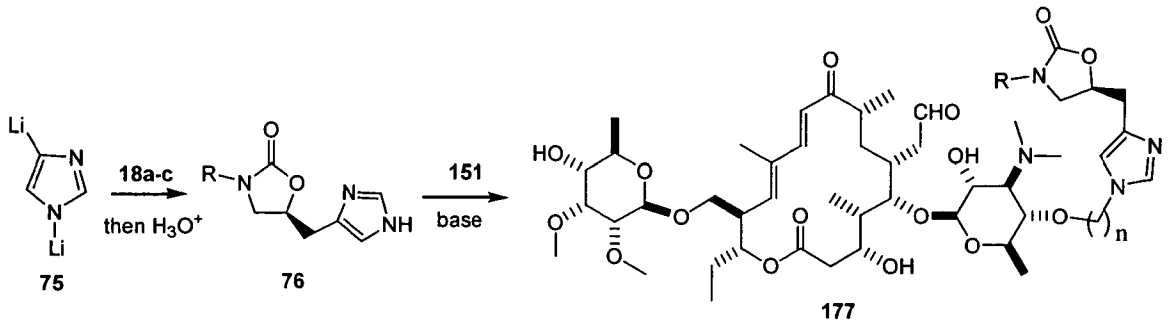
hydroxyl residues of **174** (and other sensitive functional groups of other macrolide derivatives such as intermediates **143** and **151**) can be protected with suitable protecting groups (such as those highlighted in Greene, T.W. and Wuts, P.G.M. *supra*), and the hydrogen atom on the nitrogen atom of the pyrazole derivative deprotonated with a suitable base, for example, sodium hydride or n-butyllithium. The resulting anion can then be alkylated with electrophiles **18a-c**, and the resulting product deprotected to produce targets **169**. The use of protecting groups well known to those skilled in the art for the macrolide portions of these intermediates may be required for many of the subsequent reactions shown in the schemes below that involve heteroaryl anion alkylations.

Scheme 39



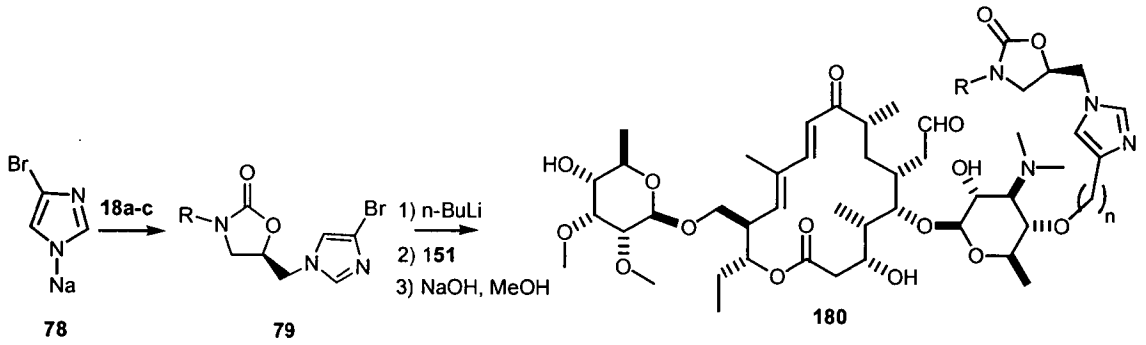
Scheme 40 exemplifies a synthesis of imidazoles of the present invention. Direct alkylation of **76** by heating with electrophiles related to **151** in an appropriate organic solvent can yield 1,4-disubstituted imidazoles **177**. Alternatively, the imidazole anion formed via deprotonation of the imidazole hydrogen atom of **76** with a suitable base and then alkylation with **151** can also produce **177**.

Scheme 40



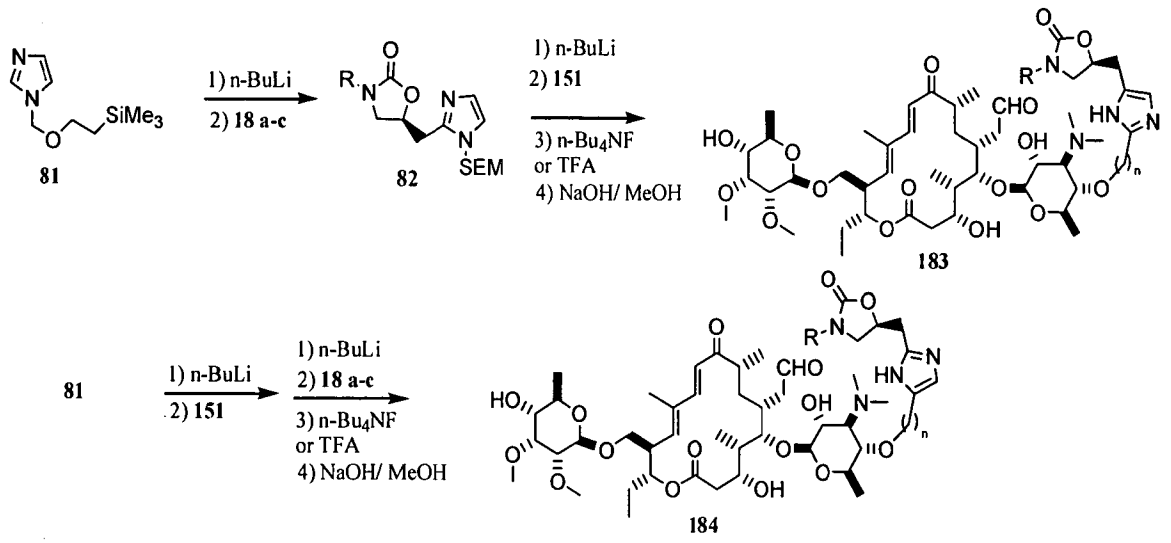
Scheme 41 illustrates another synthesis of imidazoles of the present invention. Alkylation of **78** with **18a-c** can yield bromoimidazole **79** which can then be subjected to metal-halogen exchange and alkylated with **151** (or a suitably protected derivative of **151**) to produce isomeric 1,4-disubstituted imidazoles **180**.

Scheme 41



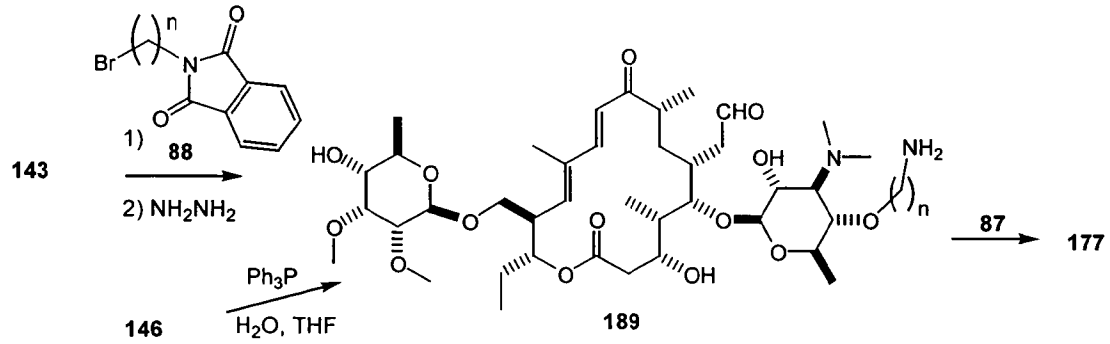
Scheme 42 depicts chemistry suitable for the synthesis of other target imidazole derivatives. Lithiation of imidazole intermediates **82** at C-4 of the imidazole, followed by alkylation with electrophiles of type **151** (or a suitably protected version such as the per-silylated derivative), and then deprotection of the SEM can produce imidazoles **183**. A reordering of steps in this process allows access to isomeric imidazoles of type **184.**

Scheme 42



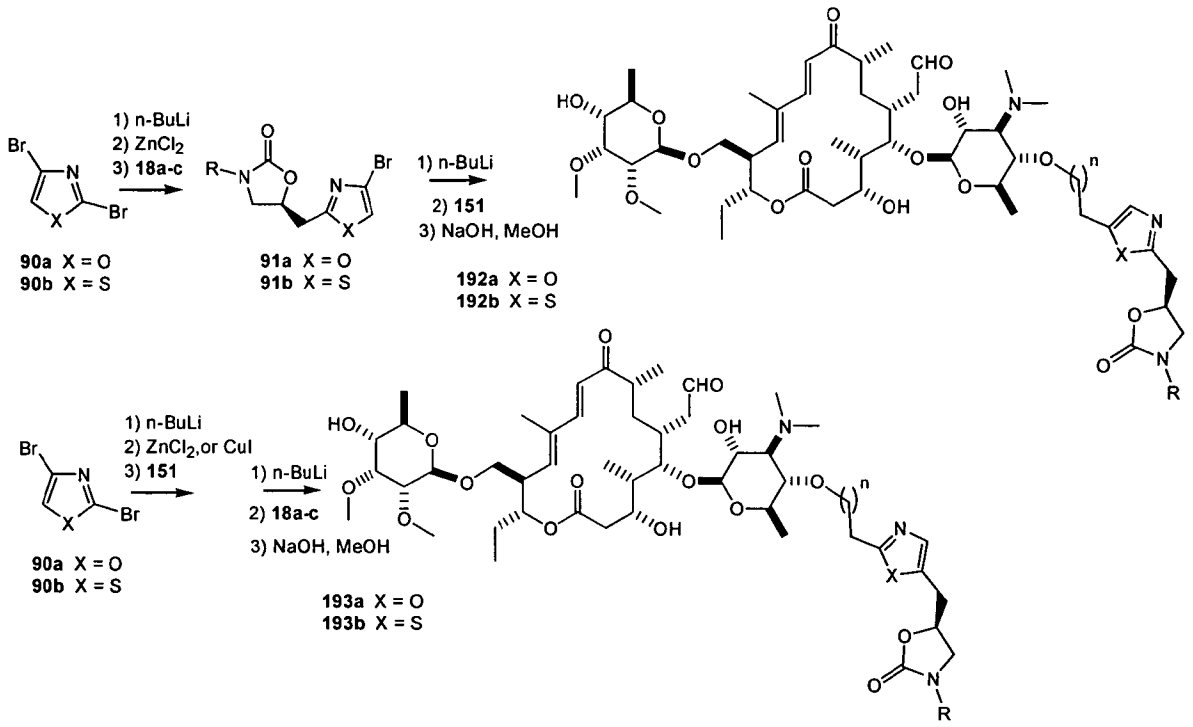
Scheme 43 shows how tosylmethyl isocyanide can be used to make imidazoles of the present invention (Vanelle *et al.*, *Eur. J. Med. Chem.*, **2000**, *35*, 157; Horne *et al.*, *Heterocycles*, **1994**, *39*, 139). The reaction of **87** (see Scheme 19) with **189** (formed via alkylation of alcohols **143** with bromoalkyl phthalimides **88** (followed by hydrazine cleavage) or reduction of azides **146**) can produce imidazoles **177**.

Scheme 43



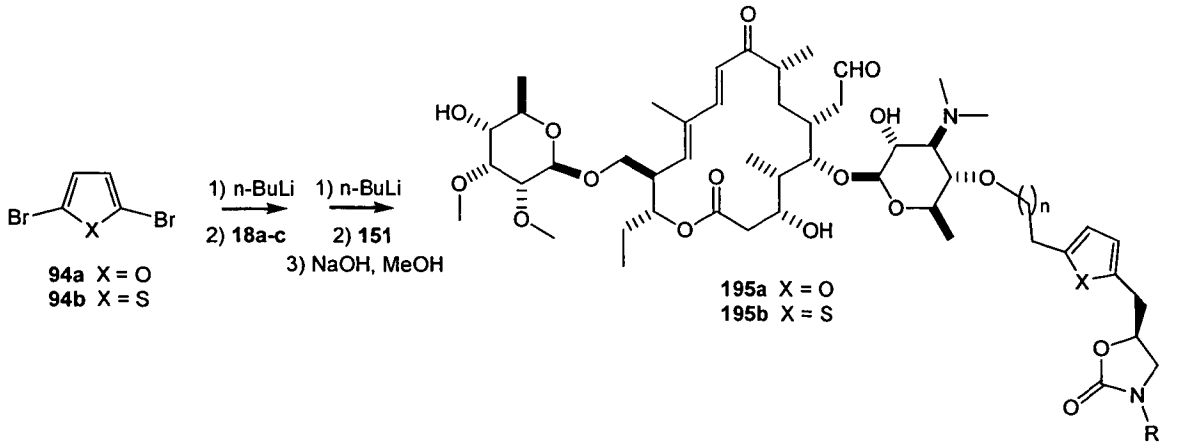
Scheme 44 delineates how 1,3 thiazole and 1,3 oxazole derivatives of the present invention can be synthesized. The bromo azoles **91** can be metallated to form the corresponding anion which can undergo alkylation with sulfonates **151** (or the related halides) to produce the final targets **192**. Reordering of the sequence of electrophiles in this process permits access to the isomeric thiazoles and oxazoles **193**.

Scheme 44



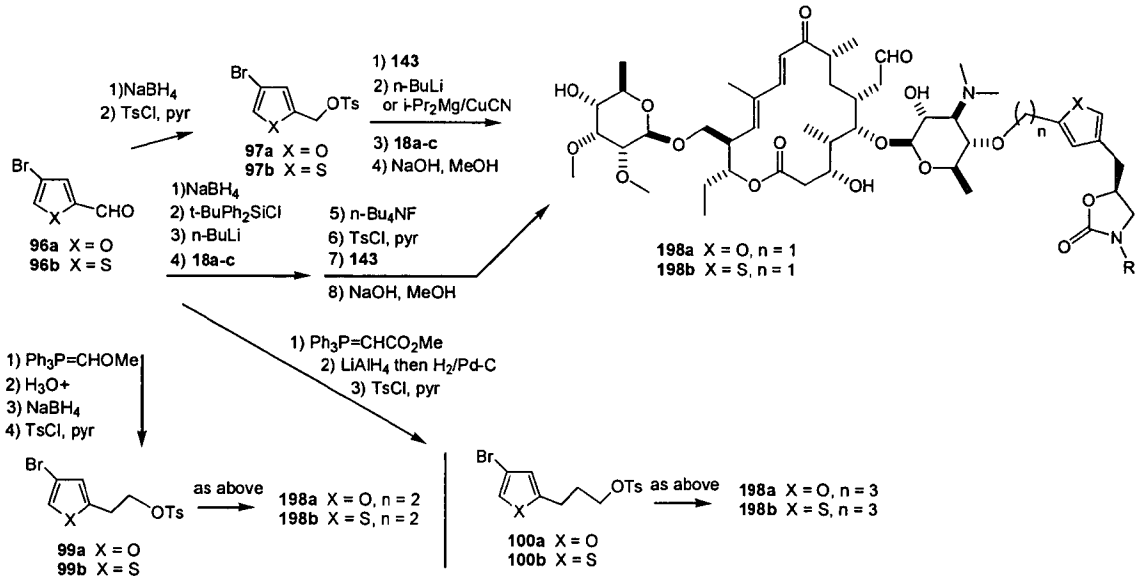
Scheme 45 shows the synthesis of 2,5 disubstituted furan and thiophene derivatives of the present invention. Commercially available dibromofuran **94a** and dibromothiophene **94b** can be monolithiated (Cherioux *et al.*, *Advanced Functional Materials*, **2001**, *11*, 305) and alkylated with electrophiles **18a-c**. The monobromo intermediates obtained from this reaction can be lithiated again and then alkylated with electrophiles of type **151** (or a protected version of **151**) to produce the final targets **195**.

Scheme 45



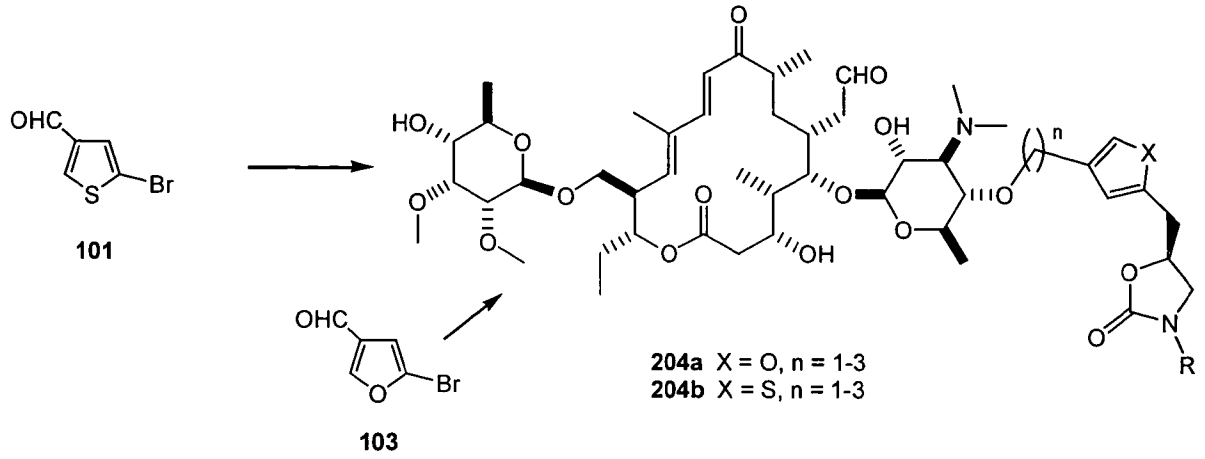
Scheme 46 depicts the synthesis of 2,4 disubstituted furan and thiophene derivatives of the present invention. The tosylates **97** (or alternate sulfonates or halides) can alkylate alcohol **143** (or a protected version thereof), and the heteroaryl bromide can be converted to a suitable organometallic agent (by reagents such as n-BuLi, or i-Pr_2Mg/CuCN). This intermediate organometallic agent can be alkylated with electrophiles **18a-c** to produce targets of type **198** where n=1. As the scheme shows, a reordering of steps can be employed involving reduction, silylation, lithiation and then initial alkylation with **18a-c**. Desilylation of the alkylation product, followed by tosylation of the alcohol, provides an intermediate that can then be alkylated with alcohol **143** to produce targets **198**. Simple homologation protocols, using the reagents depicted in Scheme **46** or others known to those skilled in the art, can convert the aldehydes **96** to longer chain tosylates such as **99** and **100**. The use of these tosylates in the alkylation with **143**, and subsequent metal-halogen exchange and alkylation with **18a-c**, can yield compounds of type **198** where n=2 and 3. Longer chain tosylates can also be produced using chemistries similar to that depicted in Scheme **46**, and other bifunctional linkers can be used to produce compounds of type **198**.

Scheme 46



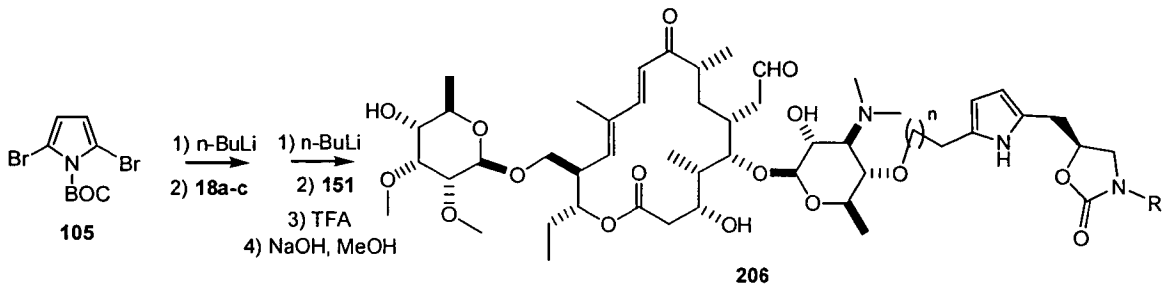
Chemistries similar to that employed above in Scheme 46 can convert known thiophene aldehyde **101** (Eras *et al.* (1984) *J. Het. Chem.* 21: 215) to produce products of type **204** (Scheme 47). Aldehyde **103** can also be converted to produce compounds of type **204**.

Scheme 47



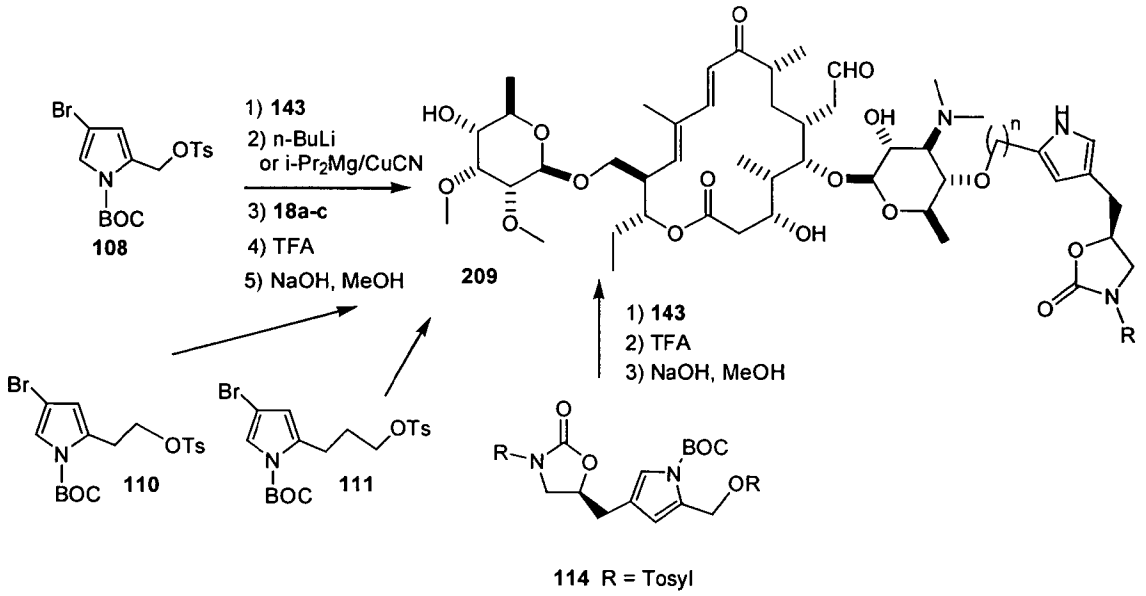
Scheme 48 illustrates the synthesis of 2,5 disubstituted pyrroles of the present invention. The BOC-protected dibromopyrrole **105** can be lithiated and alkylated sequentially (as in Scheme 24), and allowed to react with electrophiles **18a-c** and **151** (or a suitably protected analogue of **151**) to produce, after final BOC deprotection with TFA, disubstituted pyrroles of type **206**.

Scheme 48



Scheme 49 shows the synthesis of 2,4 disubstituted pyrroles of the present invention. Alcohol **143** (or a suitably protected version of **143**, formed for example by silylation of the other hydroxyl groups with bis-trimethylsilylacetamide or another silylating reagent) can be alkylated with tosylate **108** (see Scheme 28) to produce an intermediate bromopyrrole. The bromopyrrole can then be converted to an organometallic reagent that can then react with electrophiles **18a-c**. The resulting product can then be deprotected with TFA to produce pyrroles **209**. The alcohol formed after borane reduction of the acid derived from **107** can then be homologated to tosylates **110** and **111** by chemistries similar to that shown below in Scheme 51. The use of these tosylates in the alkylation strategy can produce target pyrroles of type **209** where n=2 and 3.

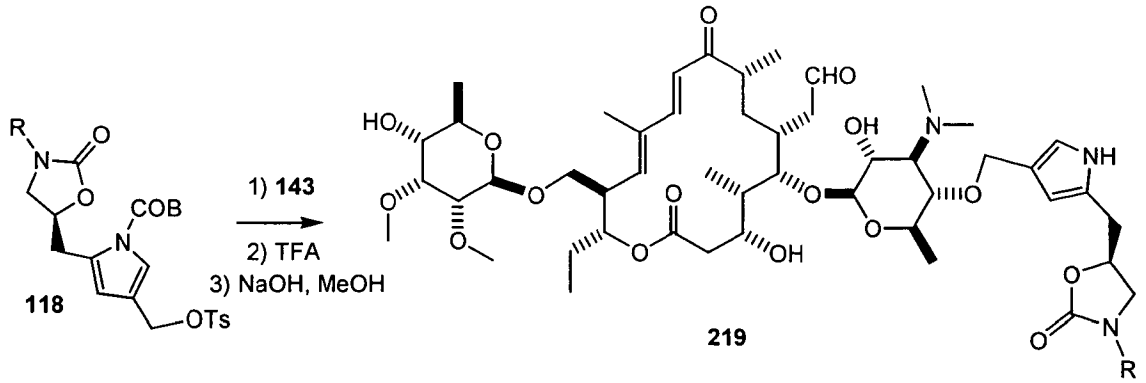
Scheme 49



An alternative approach is to protect the alcohol functions prior to tosylation, and perform the alkylation of the organometallic derived from the halopyrrole with **18a-c** first to yield **114** (see Scheme 25). Tosylate **114** provides an electrophile that can be used in the alkylation reaction with **143**. A final BOC cleavage can then give pyrroles **209**. Longer chain versions of **114** can be produced for making targets **209** where n is variable.

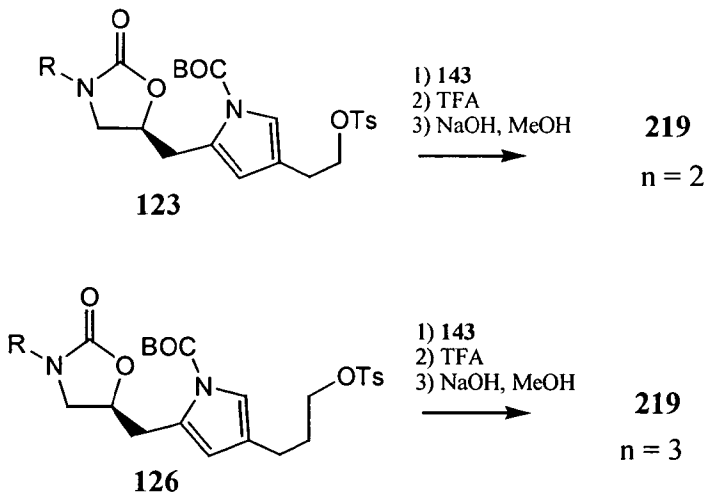
Scheme 50 shows the synthesis of isomeric 2,4 disubstituted pyrroles of the present invention. Alkylation of **143** (see Scheme 26), TFA deprotection of the BOC, and saponification of the benzoate group can yield pyrroles **219**.

Scheme 50



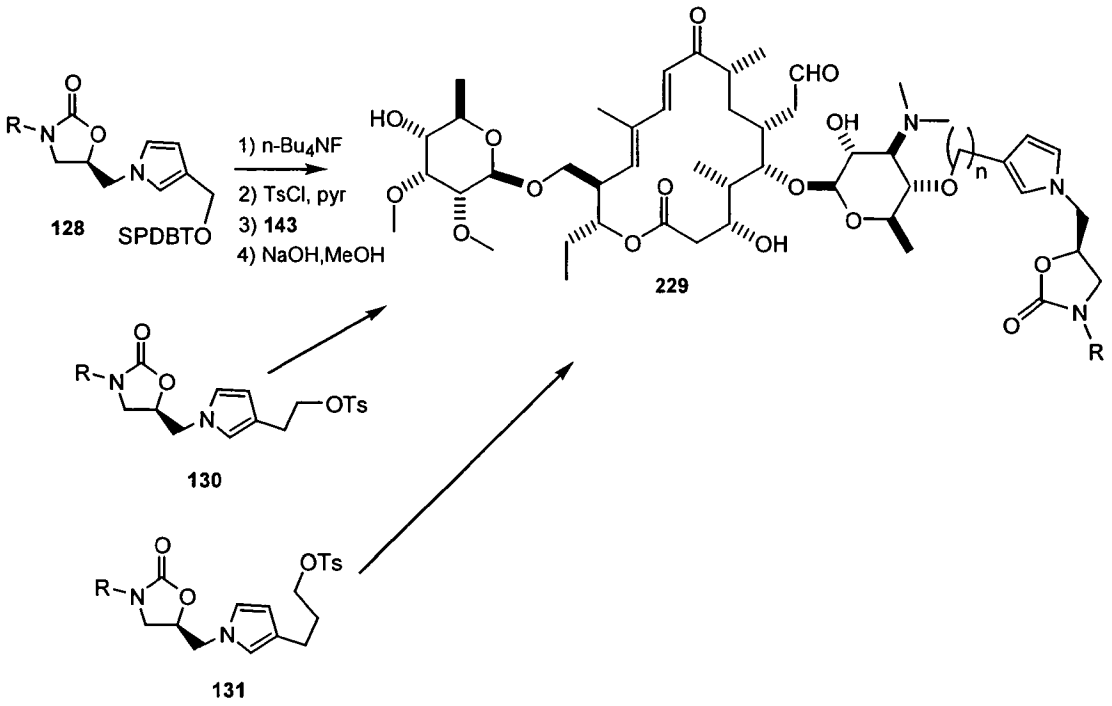
Scheme 51 illustrates the synthesis of longer chain pyrroles of type **219** using tosylates of type **123** and **126** (see Scheme 27).

Scheme 51



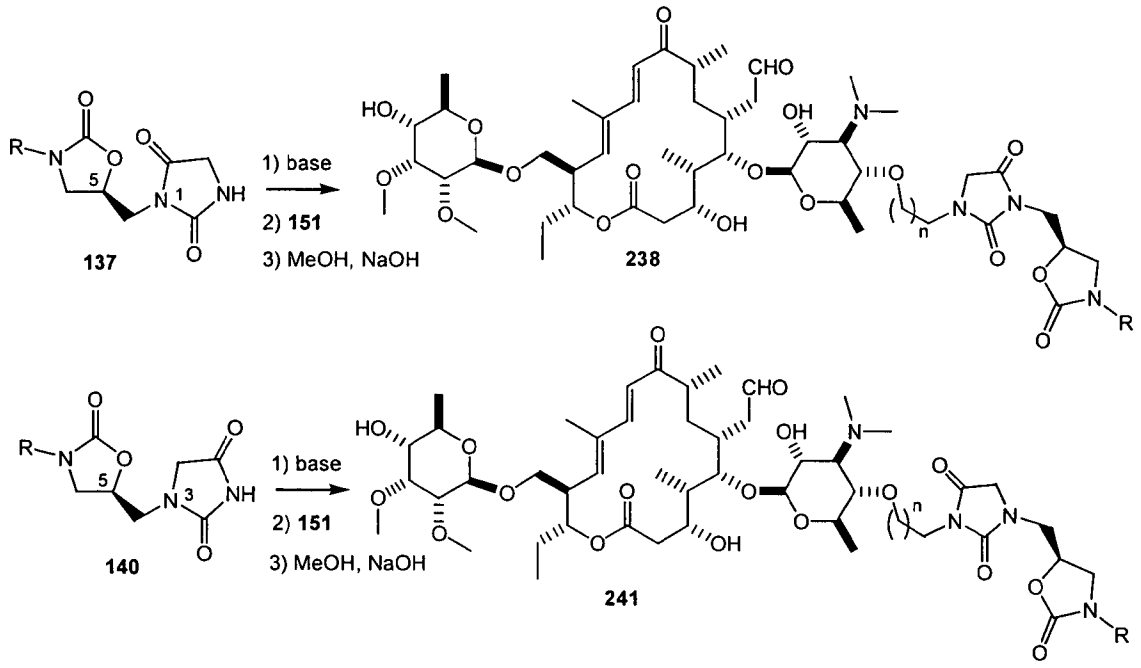
Scheme 52 shows the synthesis of 1,3 disubstituted pyrroles of the present invention. Conversion of the siloxy group of **128** (see Scheme 28) to the corresponding tosylate, followed by alkylation with alcohols of type **143** can generate the target N-substituted pyrroles **229** (where n=1). In a similar fashion, tosylates **130** and **131** can be used to produce pyrroles of type **229** (where n=2 or 3). Longer chain alkyl tosylates (and halides) can also be produced that can undergo this chemistry to produce pyrroles **229** where n is > 3.

Scheme 52



Scheme 29 above illustrates the use of hydantoin-like groups as the 5-membered heterocyclic linker, B. Another specific example of the synthesis of hydantoin derivatives of the present invention is depicted in Scheme 53. Deprotonation of **137** (see Scheme 30) with a base, for example, sodium hydride, n-butyllithium, lithium bis-trimethylsilylamide or lithium diisopropylamide, followed by alkylation with **151** (or a suitably protected derivative of **151**) can yield hydantoin targets of type **238**. The isomeric hydantoin derivatives of type **241** can be synthesized via alkylation of **140** (see Scheme 30) with **151**.

Scheme 53



In addition to the foregoing, compounds disclosed in the following publications, patents, and patent applications are suitable intermediates for preparation of the compounds of this invention: Tucker, J.A. *et al.*, *J. Med. Chem.*, **1998**, *41*, 3727; Gregory, W.A. *et al.*, *J. Med. Chem.*, **1990**, *33*, 2569; Genin, M.J. *et al.*, *J. Med. Chem.*, **1998**, *41*, 5144; Brickner, S.J. *et al.*, *J. Med. Chem.*, **1996**, *39*, 673. Barbachyn, M.R. *et al.*, *J. Med. Chem.*, **1996**, *39*, 680; Barbachyn, M.R. *et al.*, *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1003; Barbachyn, M.R. *et al.*, *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1009; Grega, K.C. *et al.*, *J. Org. Chem.*, **1995**, *60*, 5255; Park, C.-H. *et al.*, *J. Med. Chem.*, **1992**, *35*, 1156; Yu, D. *et al.*, *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 857; Weidner-Wells, M.A. *et al.*, *Bioorg. Med. Chem.*, **2002**, *10*, 2345; and Cacchi, S. *et al.*, *Org. Lett.*, **2001**, *3*, 2539; U.S. Patent Nos. 4,801,600; 4,948, 801; 5,736,545; 6,362,189; 5,523,403; 4,461,773; 6,365,751; 6,124,334; 6,239,152; 5,981,528; 6,194,441; 6,147,197; 6,034,069; 4,990,602; 6,124,269; and 6,271,383; U.S. Patent Application Publication No. 2001/0046992; International Publication Nos. WO 96/15130; WO 95/14684; WO 99/28317; WO 98/01447; WO 98/01446; WO 97/31917; WO 97/27188; WO 97/10223; WO 97/09328; WO 01/46164; WO 01/09107; WO 00/73301; WO 00/21960; WO 01/81350; WO 97/30995; WO 99/10342; WO 99/10343; WO 99/64416; WO 00/232917; and WO 99/64417; and European Patent Nos. EP 0312000 B1; EP 0359418 A1; EP 0345627; EP 1132392; and EP 0738726 A1.

4. Characterization of Compounds of the Invention

Compounds designed, selected and/or optimized by methods described above, once produced, may be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules may be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

Furthermore, high-throughput screening may be used to speed up analysis using such assays. As a result, it may be possible to rapidly screen the molecules described herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agents. Also, it may be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein synthesis using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

(1) *Surface Binding Studies.* A variety of binding assays may be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) that can be used to evaluate the binding properties molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

SPR methodologies measure the interaction between two or more macromolecules in real-time through the generation of a quantum-mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscatawy, N.J.) provides a focused beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel" composed of carboxylated dextran that provides a matrix for the covalent immobilization of analytes of interest is attached to the gold film. When the focused light interacts with the free electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is spectrally depleted in wavelengths that optimally evolved the resonance. By separating the reflected polychromatic light into its component wavelengths (by means of a prism), and determining the frequencies that are depleted, the BIAcore establishes an optical interface which accurately reports the behavior of the generated surface plasmon resonance. When designed as

above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided through the buffer compartment, the interaction between the two components can be measured in real time based on the accumulation of mass in the evanescent field and its corresponding effects of the plasmon resonance as measured by the depletion spectrum. This system permits rapid and sensitive real-time measurement of the molecular interactions without the need to label either component.

(2) *Fluorescence Polarization.* Fluorescence polarization (FP) is a measurement technique that can readily be applied to protein-protein, protein-ligand, or RNA-ligand interactions in order to derive IC_{50}s and Kds of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a fluorophore. This is generally the smaller molecule in the system (in this case, the compound of interest). The sample mixture, containing both the ligand-probe conjugate and the ribosome, ribosomal subunit or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe fluorophores, and re-emitted a short time later. The degree of polarization of the emitted light is measured. Polarization of the emitted light is dependent on several factors, but most importantly on viscosity of the solution and on the apparent molecular weight of the fluorophore. With proper controls, changes in the degree of polarization of the emitted light depends only on changes in the apparent molecular weight of the fluorophore, which in-turn depends on whether the probe-ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on FP have a number of important advantages, including the measurement of IC_{50}s and Kds under true homogenous equilibrium conditions, speed of analysis and amenity to automation, and ability to screen in cloudy suspensions and colored solutions.

(3) *Protein Synthesis.* It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest may also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays may be performed by administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and

inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of ^{3}H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of protein synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is a inhibitor of protein synthesis.

Furthermore, the compounds may be assayed for anti-proliferative or anti-infective properties on a cellular level. For example, where the target organism is a microorganism, the activity of compounds of interest may be assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition may be indicative that the molecule may be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens may be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays may be performed in microtiter trays according to conventional methodologies as published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS. M7-A5-Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9).

5. Formulation and Administration

The compounds of the invention may be useful in the prevention or treatment of a variety of human or other animal disorders, including for example, bacterial infection, fungal infections, viral infections, parasitic diseases, and cancer. It is contemplated that, once identified, the active molecules of the invention may be incorporated into any suitable carrier prior to use. The dose of active molecule, mode of administration and use of suitable carrier will depend upon the intended recipient and target organism. The formulations, both for veterinary and for human medical use, of compounds according to the present invention typically include such compounds in association with a pharmaceutically acceptable carrier.

The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, anti-bacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified or designed according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

A pharmaceutical composition of the invention should be formulated to be compatible with its intended route of administration. Examples of routes of administration include oral or parenteral, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Remington's Pharmaceutical Sciences, (Gennaro, A., ed.), Mack Pub., (1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Suppositories for rectal administration also can be prepared by mixing the drug with a non-

irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, and hydrogenated naphthalenes. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration may be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; a powder or granular composition; a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion. The drug may also be administered in the form of a bolus, electuary or paste. A tablet may be made by compressing or moulding the drug optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes;

a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the drug that may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the drug for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap. Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations can be used.

For inhalation treatments, inhalation of powder (self-propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a fine powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (*i.e.,* being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.,* a gas such as carbon dioxide, or a nebulizer.

Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

The active compounds may be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can

be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore, administration can be by periodic injections of a bolus, or can be made more continuous by intravenous, intramuscular or intraperitoneal administration from an external reservoir (*e.g.,* an intrvenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen-thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs can be formulated for parenteral or oral administration to humans or other mammals, for example, in therapeutically effective amounts, *e.g.,* amounts that provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from the donor. The compound can be provided to the donor host. Alternatively or, in addition, once removed from the donor, the organ or living tissue can be placed in a preservation solution containing the active compound. In all cases, the active compound can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For

example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution.

Active compound as identified or designed by the methods described herein can be administered to individuals to treat disorders (prophylactically or therapeutically). In conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

In therapeutic use for treating, or combating, bacterial infections in mammals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level or tissue level of active component in the animal undergoing treatment which will be anti-microbially effective. The term "effective amount" is understood to mean that the compound of the invention is present in or on the recipient in an amount sufficient to elicit biological activity, for example, anti-microbial activity, anti-fungal activity, anti-viral activity, anti-parasitic activity, and/or anti-proliferative activity. Generally, an effective amount of dosage of active component will be in the range of from about 0.1 to about 100, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, for example, two to four times per day.

6. Examples

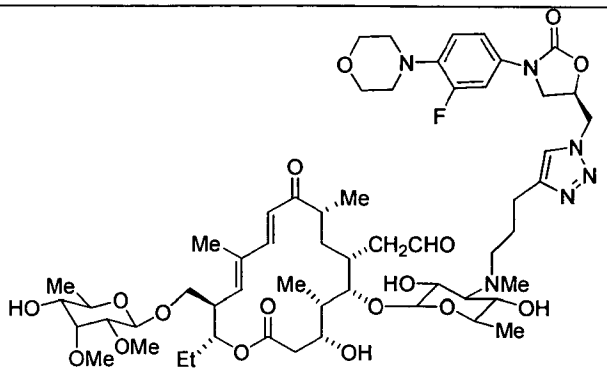
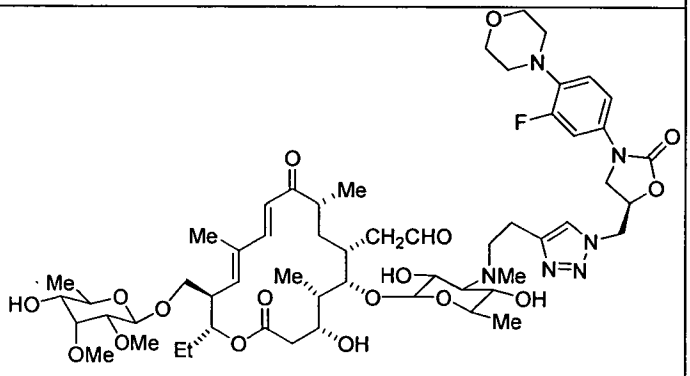
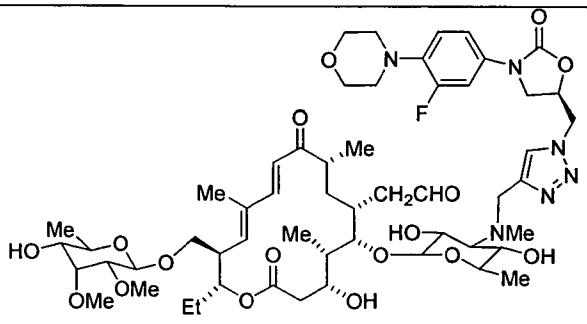
Some of the abbreviations used in the following experimental details of the synthesis of the examples are defined below:

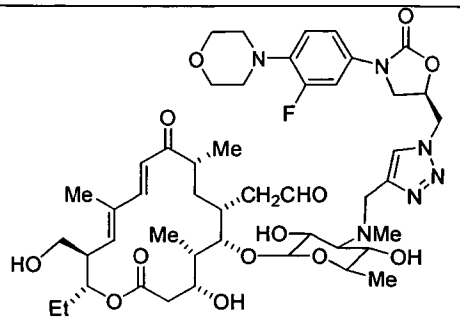
hr	=	hour(s)
min	=	minute(s)
mol	=	mole(s)
mmol	=	millimole(s)
M	=	molar
μM	=	micromolar
g	=	gram(s)
μg	=	microgram(s)
rt	=	room temperature
L	=	liter(s)
mL	=	milliliter(s)
Et_2O	=	diethyl ether
THF	=	tetrahydrofuran
DMSO	=	dimethyl sulfoxide
EtOAc	=	ethyl acetate
Et_3N	=	triethylamine
CH_2Cl_2	=	methylene chloride
$CHCl_3$	=	chloroform
CCl_4	=	carbon tetrachloride
MeOH	=	methanol
DMF	=	dimethylformamide
BOC	=	t-butoxycarbonyl
TFA	=	trifluoroacetic acid
DBU	=	diazabicycloundecene
TBDPSCl	=	t-butyldiphenylchlorosilane

Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance 300 or Avance 500 spectrometer, or in some cases a GE-Nicolet 300 spectrometer. Common reaction solvents were either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and anhydrous as obtained from the manufacturer unless otherwise noted. "Chromatography" or "purified by silica gel" refers to flash column chromatography using silica gel (EM Merck, Silica Gel 60, 230-400 mesh) unless otherwise noted.

Compounds synthesized in accordance with the invention are listed in Table 2.

TABLE 2

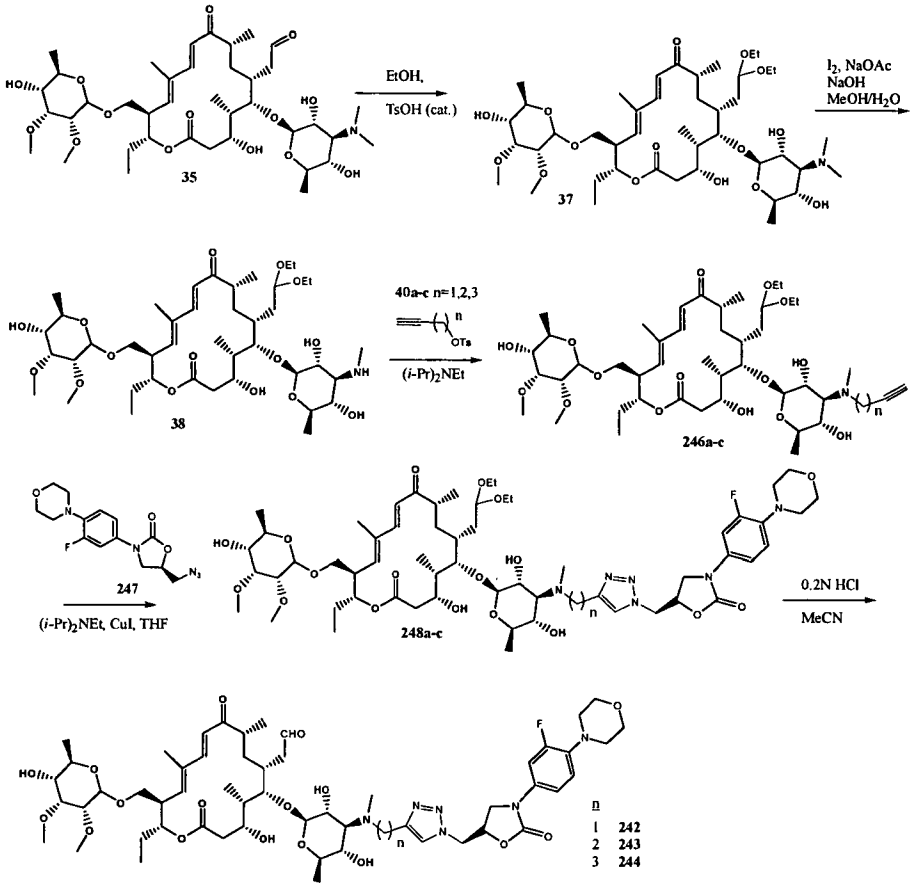
Compound #	Structure
242	
243	
244	

245	

Example 1 – Synthesis of Compounds 242-244

Scheme 54 below depicts the synthesis of compounds **242-244** using the chemistries previously exemplified. Briefly, desmycosin was protected as its diethylacetal derivative **37**. Demethylation under standard conditions (US 3,725,385) gave desmethyl derivative **38**. This amine was alkylated with tosylates **40a-c** to give alkynes **246a-c** wherein n is 1, 2, or 3 respectively. Alkynes **246a-c** were reacted with azide intermediate **247** (Brickner, S.J. *et al.*, *J. Med. Chem.*, **1996**, *39*, 673) in the presence of Cu(I)I to produce compounds **247a-c**. Subsequent hydrolysis of the diethylacetal protecting group afforded compounds **242**, **243**, and **244**.

Scheme 54



Synthesis of diethylacetal 37

To a solution of 1.00 g (1.30 mmol) of desmycosin in 10 mL of ethyl alcohol was added 0.260 g (1.36 mmol) of *p*-toluenesulfonic acid at ambient temperature. The reaction mixture was allowed to stir for 3 h, diluted with 30 mL of saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 1.220 g of **37**, which was used without further purification.

Synthesis of desmethyl compound 38

To a mixture of 0.250 g (0.29 mmol) of **37** and 0.486 g (5.92 mmol) of NaOAc in 10 mL of $MeOH/H_2O$ (80% MeOH) at 55°C was added 0.075 g (0.29 mmol) of solid iodine. The pH of the reaction mixture was maintained at 9 by addition of 1 N NaOH at time intervals of 10, 30, and 60 minutes after the addition of iodine. The reaction mixture was stirred at 55°C for 1 h following the last addition of NaOH solution, then diluted with 25 mL of saturated $NaHCO_3$ and

extracted with EtOAc (50 mL x 2). The combined EtOAc extracts were washed sequentially with 15 mL of 5% NaS_2O_4 and brine, dried over $MgSO_4$, filtered, and concentrated to give 0.221 g of **38**.

Synthesis of toluene-4-sulfonic acid but-3-ynyl ester 40b

3-Butyn-1-ol (1.8 g, 25 mmol) was dissolved in methylene chloride (CH_2Cl_2) (40 mL) and triethylamine (Et_3N) (4.18 mL, 30 mmol). The solution was stirred at 0°C followed by addition of p-toluenesulfonyl chloride (5.05 g, 26.25 mmol). The reaction was allowed to warm to room temperature over a period of 1 hour and stirring was continued overnight. Thin layer chromatography (TLC) analysis (hexanes/EtOAc 6:1) after 20 hours of reaction showed a complete consumption of 3-butyn-1-ol. The precipitated triethylamine hydrochloride was filtered off and the filtrate washed with water (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated away to give a light-yellow oil (5.45 g, 97%). The crude oil was used without further purification; however, it could be purified on a silica gel column, first eluting with 8% EtOAc in hexanes followed by 40% EtOAc in hexanes.

Synthesis of toluene-4-sulfonic acid prop-2-ynyl ester 40a

Tosylate **40a** was made from propargyl alcohol and tosyl chloride as described for tosylate **40b** above.

Synthesis of toluene-4-sulfonic acid pent-4-ynyl ester 40c

Tosylate **40c** was made from 3-pentyn-1-ol and tosyl chloride as described for tosylate **40b** above.

Synthesis of alkyne 246b

A mixture of 0.200 g (0.24 mmol) of **38**, 0.270 g (1.20 mmol) of 3-butyn-1-ol tosylate **40b**, 0.311 g (2.41 mmol) of di-isopropylethylamine and 10 mg of dimethylaminopyridine in 5 mL of THF was allowed to stir at 55 °C for 48 h. The mixture was diluted with 20 mL of saturated $NaHCO_3$, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to give 0.065 g of desired product

246b and 0.063 g of recovered starting material **38** after purification through flash column chromatography on silica gel.

Synthesis of alkyne 246a

Alkyne **246a** was made from tosylate **40a** and desmethyl compound **38** as described for alkyne **246b** above.

Synthesis of alkyne 246c

Alkyne **246c** was made from tosylate **40c** and desmethyl compound **38** as described for alkyne **246c** above.

Synthesis of triazole 243

To a 5 mL THF solution of 0.065 g (0.074 mmol) of alkyne **246b**, 0.047 g (0.15 mmol) of azide 247, and 0.28 g (2.21 mmol) of diisopropylethylamine was added 0.028 g (0.15 mmol) of CuI at ambient temperature. The reaction mixture was stirred at 25°C for 10 h, diluted with 50 mL of CH_2Cl_2, washed sequentially with saturated NH_4Cl (15 mL x 2), brine, dried over $MgSO_4$, filtered, and concentrated to give a white solid which was purified by silica gel chromatography to afford 0.080 g of compound **248b**. This material was dissolved in 2 mL of 0.2 N $HCl_{(aq)}$/MeCN (1:1) and stirred at 25°C for 4 h. The reaction mixture was diluted with 60 mL of EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to give 0.041 g of the desired product triazole **243**. (Partial ^{1}H NMR data in $CDCl_3$): 9.69 (s, 1 H), 7.58 (s, 1 H), 7.46 ~ 6.86 (series of multiple peaks, 5 H), 6.27(d, J = 17.3 Hz, 1 H), 5.91 (d, J = 9.4 Hz, 1 H), 5.01(m, 1 H), 2.43 (s, 3 H).

Synthesis of triazole 242

Triazole **242** was made from alkyne **246a** and azide **247** as described for triazole **243** above (50% yield). (Partial ^{1}H NMR data, 300 MHz, $CDCl_3$) δ 9.73 (s, 1 H), 7.55 (s, 1 H), 7.28 ~ 6.80 (series of multiple peaks, 5 H), 6.20(d, J = 15.0 Hz, 1 H), 5.91 (d, J = 9.0 Hz, 1 H), 5.00 (m, 1 H), 2.41 (s, 3 H).

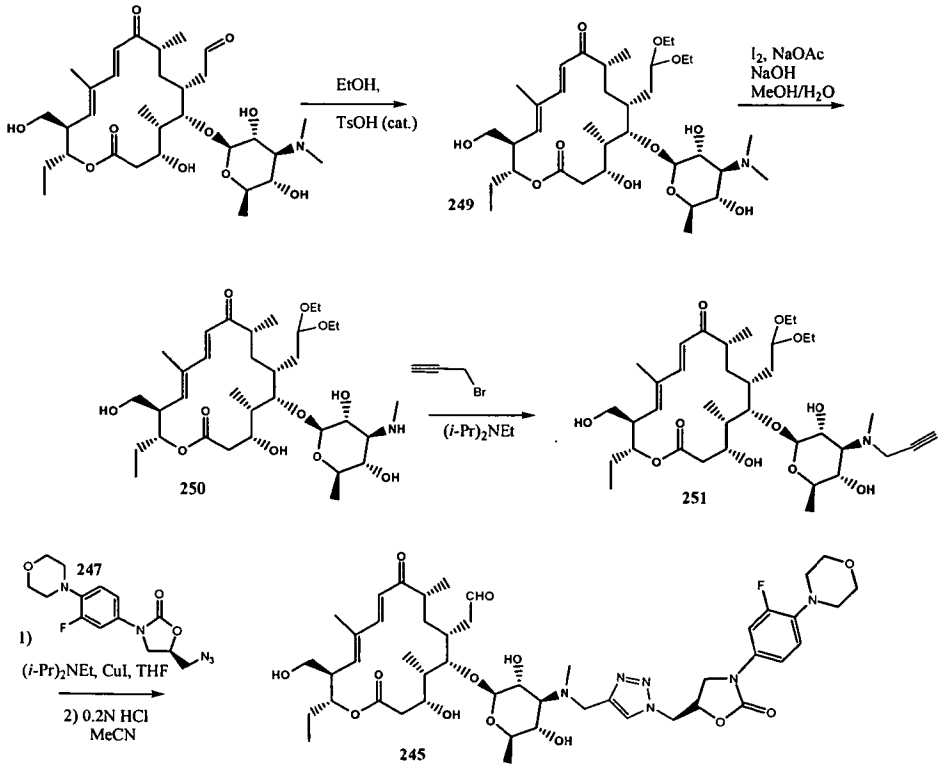
Synthesis of triazole 244

Triazole **244** was made from alkyne **246c** and azide **247** as described for triazole **243** above (62% yield). (Partial ^{1}H NMR data, 300 MHz, $CDCl_3$) δ 9.69 (s, 1 H), 7.69 (s, 1 H), 7.54 ~ 6.89 (series of multiple peaks, 5 H), 6.26 (d, J = 15.4 Hz, 1 H), 5.92 (d, J = 9.7 Hz, 1 H), 5.03 (m, 1 H), 4.56 (d, J = 7.7 Hz, 1 H), 2.38 (s, 3 H).

Example 2 – Synthesis of Compound 245

The known compound, 5-*O*-myamarosyl-tylonolide (OMT), may be treated with chemistry analogous to that presented in Scheme 54 to afford new compounds such as **245.** More specifically, as shown in Scheme 55, OMT may be protected as its diethylacetal derivative **250**, and subsequent demethylation gives amine **251**. Alkylation with propargyl bromide then provides alkyne **252**. Reaction of alkyne **252** and azide **248** followed by deprotection of the aldehyde moiety provides triazole **245**.

Scheme 55



Synthesis of diethylacetal 249

To a solution of 0.410 g (0.68 mmol) of OMT in 10 mL of ethyl alcohol was added 0.137 g (0.72 mmol) of *p*-toluenesulfonic acid at ambient temperature. The reaction mixture was allowed to stir for 4 h, diluted with 20 mL of saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined EtOAc layers were washed with brine, dried over $MgSO_4$, and concentrated to give 0.470 g of the desired product **249**.

Synthesis of desmethyl compound 250

To a mixture of 0.150 g (0.22 mmol) of **249** and 0.367 g (4.47 mmol) of NaOAc in 10 mL of MeOH/H_2O (80% MeOH) at 55°C was added 0.057 g (0.22 mmol) of solid iodine. The pH of the reaction mixture was maintained at about 9 through the addition of 1 N NaOH at the time intervals of 10, 30, and 60 minutes after the addition of iodine. The reaction mixture was stirred at 55°C for another hour following the last addition of NaOH solution, then diluted with 25 mL of saturated $NaHCO_3$, and extracted with EtOAc (50 mL x 2). The combined EtOAc layers were washed sequentially with 15 mL of 5% NaS_2O_4, brine, dried over $MgSO_4$, filtered, and concentrated to give 0.130 g of desired product **250**.

Synthesis of alkyne 251

A mixture of 0.058 g (0.088 mmol) of **250**, 0.012 g (0.097 mmol) of propargyl bromide, 0.342 g (2.65 mmol) of di-isopropylethylamine 5 mL of THF was stirred at 55°C for 24 h. The mixture was diluted with 20 mL of saturated $NaHCO_3$, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give 0.050 g of alkyne **251** after purification by silica gel flash column chromatography.

Synthesis of triazole 245

To a 5mL THF solution of 0.050 g (0.072 mmol) of **251**, 0.046 g (0.14 mmol) of azide **247**, and 0.279 g (2.16 mmol) of di-iospropylethylamine was added 0.027 g (0.14 mmol) of CuI at ambient temperature. The reaction mixture was stirred at 25°C for 4 h, diluted with 50 mL of CH_2Cl_2, washed sequentially with saturated NH_4Cl (15 mL x 2), brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel flash column chromatography to give 0.067 g of a solid. This material was dissolved in 2 mL of 0.2 N HCl/MeCN (1:1) and stirred at 25°C for 4

h. The reaction mixture was diluted with 60 mL of EtOAc, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to give 0.019 g of triazole **245**. (Partial ^1H NMR data in $CDCl_3$): 9.70 (s, 1 H), 7.74 (s, 1 H), 7.36 ~ 6.89 (series of multiple peaks), 6.28(d, J = 15.4 Hz, 1 H), 5.95 (d, J = 10.34 Hz, 1 H), 5.05(m, 1 H), 2.38 (s, 3 H).

INCORPORATION BY REFERENCE

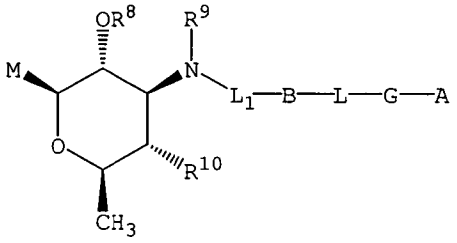
The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

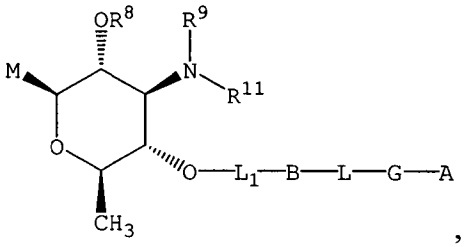
The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A compound having the formula:



or



,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

A is selected from H, R^2, phenyl-R^2, and pyridyl-R^2, wherein the phenyl and pyridyl groups are substituted with 0-2 R^1 groups;

R^1, at each occurrence, is selected from H, F, Cl, Br, I, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $(CR^3R^3)_rCF_3$, $(CR^3R^3)_rCN$, $(CR^3R^3)_rNO_2$, $(CR^3R^3)_rNR^3R^3$, $(CR^3R^3)_rOR^3$, $(CR^3R^3)_rS(O)_pR^3$, $(CR^3R^3)_rC(O)R^3$, $(CR^3R^3)_rC(O)OR^3$, $(CR^3R^3)_rOC(O)R^3$, $(CR^3R^3)_rNR^3C(O)R^3$, $(CR^3R^3)_rC(O)NR^3R^3$, $(CR^3R^3)_rC(=NR^3)R^3$, $(CR^3R^3)_rNR^3C(O)NR^3R^3$, $(CR^3R^3)_rNR^3S(O)_pR^3$, $(CR^3R^3)_rS(O)_pNR^3R^3$, $(CR^3R^3)_rNR^3S(O)_pNR^3R^3$, $(CR^3R^3)_r$-$C_{3\text{-}10}$ saturated, unsaturated, or aromatic carbocycle substituted with 0-1 R^3 groups, and a $(CR^3R^3)_r$-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-3 R^3 groups;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, and 2;

R^2 is selected from R^4, $C_{1\text{-}8}$ alkyl substituted with 0-4 R^4 groups, $C_{2\text{-}8}$ alkenyl substituted with 0-4 R^4 groups, $C_{2\text{-}8}$ alkynyl substituted with 0-4 R^4 groups, $C_{3\text{-}12}$ carbocycle substituted with 0-4 R^4 groups, and 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-4 R^4 groups;

R^3, at each occurrence, is selected from H, $C_{1\text{-}4}$ alkyl, phenyl, and benzyl;

alternatively, NR^3R^3 comprises a 3-6 membered saturated, unsaturated, or aromatic heterocycle containing the nitrogen atom to which the R^3 groups are attached and optionally containing one or more oxygen, nitrogen, and sulfur atoms;

B is a 5-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-2 carbonyl groups and 0-2 R^4 groups;

R^4, at each occurrence, is selected from H, =O, F, Cl, Br, I, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^6 groups, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^6 groups, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^6 groups, $(CR^3R^5)_rCF_3$, $(CR^3R^5)_rCN$, $(CR^3R^5)_rNO_2$, $(CR^3R^5)_rNR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rOR^6$, $(CR^3R^5)_rS(O)_p(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(O)(CR^3R^3)_tR^6$, $(CR^3R^5)_rOC(O)(CR^3R^3)_tR^6$, $(CR^3R^5)_rSC(O)(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(O)O(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3C(O)(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(O)NR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(O)NR^{4a}(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(=NR^3)(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(=NNR^{4a}R^{4a})(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(=NNR^3C(O)R^{4a})(CR^3R^3)_tR^6$, $(CR^3R^5)_rC(=NOR^6)(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3C(O)O(CR^3R^3)_tR^6$, $(CR^3R^5)_rOC(O)NR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3C(O)NR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3S(O)_p(CR^3R^3)_tR^6$, $(CR^3R^5)_rS(O)_pNR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_rNR^3S(O)_pNR^3(CR^3R^3)_tR^6$, $(CR^3R^5)_r$-$C_{3\text{-}10}$ saturated, unsaturated, or aromatic carbocycle substituted with 0-3 R^6 groups, and $(CR^3R^5)_r$-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-3 R^6 groups;

alternatively, two R^4 groups may form $-O(CH_2)_sO-$;

R^{4a}, at each occurrence, is selected from H, $C_{1\text{-}8}$ alkyl, $C_{3\text{-}8}$ cycloalkyl, $(CH_2)_uOR^3$, and $(CH_2)_vNR^3R^3$;

alternatively, $NR^{4a}R^{4a}$ comprises a 5-6 membered saturated, unsaturated, or aromatic heterocycle containing the nitrogen atom to which the R^{4a} groups are attached and optionally containing one or more oxygen, nitrogen, and sulfur atoms, and substituted with 0-1 R^7 groups;

s, at each occurrence, is selected from 1, 2, 3, or 4;

t, at each occurrence, is selected from 0, 1, or 2;

u, at each occurrence, is selected from 1, 2, 3, 4, or 5;

v, at each occurrence, is selected from 0, 1, 2, or 3;

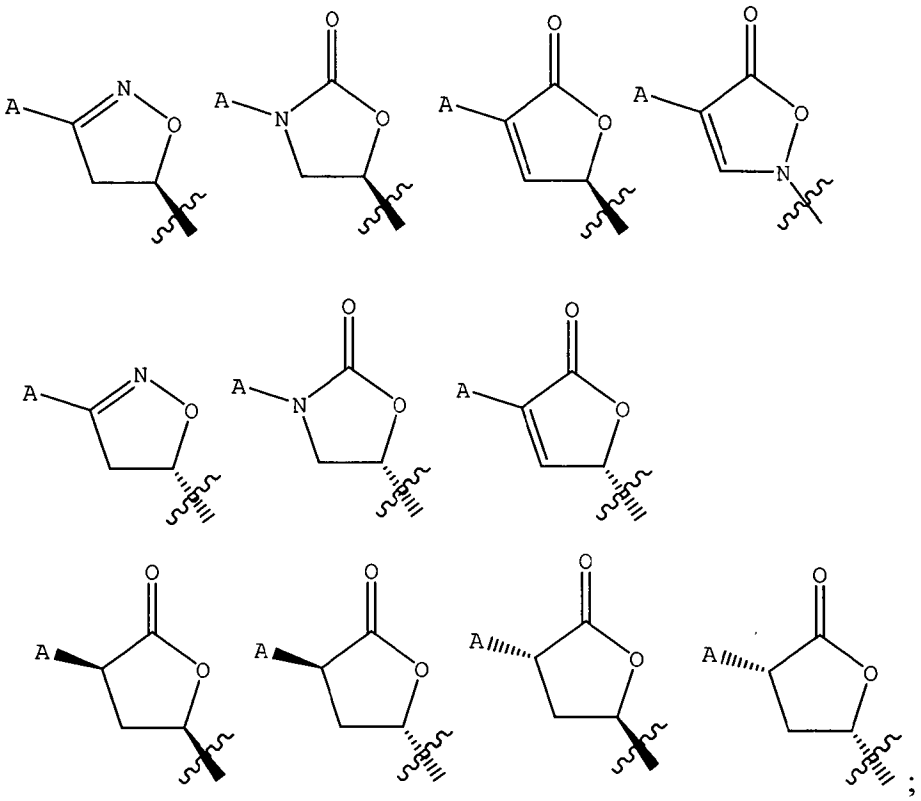
R^5, at each occurrence, is selected from H, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^7, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^7, and $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^7;

alternatively, CR^3R^5 comprises a carbonyl group;

R^6, at each occurrence, is selected from R^7, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^7 groups, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^7 groups, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^7 groups, $(CR^3R^5)_r$-$C_{3\text{-}10}$ saturated, unsaturated, or aromatic carbocycle substituted with 0-3 R^7 groups, and $(CR^3R^5)_r$-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-3 R^7 groups;

R^7, at each occurrence, is selected from H, =O, F, Cl, Br, I, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $(CR^3R^3)_rCF_3$, $(CR^3R^3)_rCN$, $(CR^3R^3)_rNO_2$, $(CR^3R^3)_rNR^3R^3$, $(CR^3R^3)_rOR^3$, $(CR^3R^3)_rS(O)_pR^3$, $(CR^3R^3)_rC(O)R^3$, $(CR^3R^3)_rC(O)OR^3$, $(CR^3R^3)_rOC(O)R^3$, $(CR^3R^3)_rNR^3C(O)R^3$, $(CR^3R^3)_rC(O)NR^3R^3$, $(CR^3R^3)_rC(=NR^3)R^3$, $(CR^3R^3)_rNR^3C(O)NR^3R^3$, $(CR^3R^3)_rNR^3S(O)_pR^3$, $(CR^3R^3)_rS(O)_pNR^3R^3$, $(CR^3R^3)_rNR^3S(O)_pNR^3R^3$, $(CR^3R^3)_r$-$C_{3\text{-}10}$ saturated, unsaturated, or aromatic carbocycle substituted with 0-1 R^3 groups, and $(CR^3R^3)_r$-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms and substituted with 0-3 R^3 groups;

G-A is selected from:

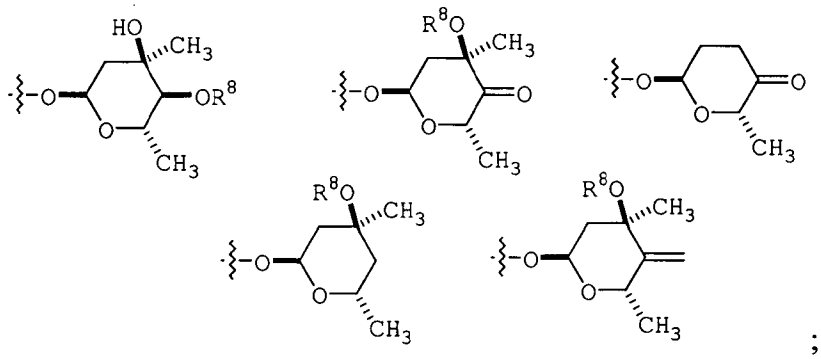


;

R^8, at each occurrence, is selected from H and C(O)-C_{1-5} alkyl;

R^9 is selected from H, C_{1-4} alkyl, and C(O)-C_{1-5} alkyl;

R^{10} is OH or is selected from:



;

R^{11} is selected from H and C_{1-4} alkyl;

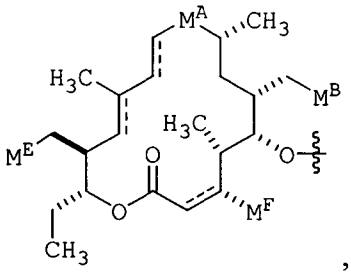
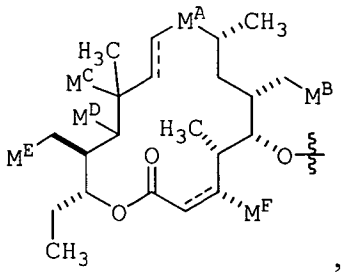
L is selected from -CH_2-, -C(O)-, -C(S)-, -C(=NOR^{12})-, -CH_2CH_2-, -OCH_2-, -SCH_2-, -S(O)CH_2-, -$S(O)_2CH_2$-, -$NR^{12}CH_2$-, -C(O)CH_2-, -C(S)CH_2-, and -C(=NOR^{12})CH_2-;

R^{12} is selected from H, C_{1-8} alkyl, C_{3-8} cycloalkyl, $(CH_2)_uOR^3$, and $(CH_2)_vNR^3R^3$;

L_1 is selected from $-CH_2-L_{1A}-$ and $-C(O)-L_{1A}-$;

L_{1A} is absent or is selected from C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl wherein 0-2 carbon atoms of L_{1A} are replaced by a heteroatom selected from oxygen, nitrogen, and sulfur, and L_{1A} is substituted with 0-1 carbonyl groups and 0-2 groups selected from C_{1-4} alkyl, OR^3, and NR^3R^3;

M is selected from: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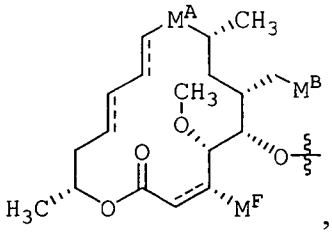
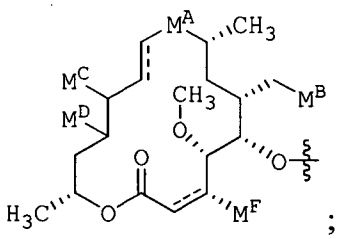
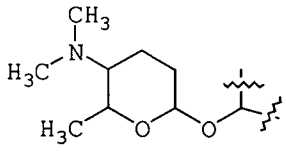

, and

;

wherein ═ is a carbon-carbon single bond or a carbon-carbon double bond;

M^A is selected from $-CH_2-$, $-C(O)-$, $-C(O)-N(R^{13})-$, $-CH(NR^{13}R^{14})-$, $-C(=NOR^{13})-$, $-C(=N-NR^{13}R^{14})-$, $-CH(-OR^{13})-$, and


;

R^{13} is selected from H, C_{1-6} alkyl substituted with 0-2 R^4 groups, C_{2-6} alkenyl substituted with 0-2 R^4 groups, C_{2-6} alkynyl substituted with 0-2 R^4 groups, C_{6-10} saturated, unsaturated, or aromatic carbocycle substituted with 0-2 R^4 groups, and 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms, and substituted with 0-2 R^4 groups;

R^{14} is selected from H, C_{1-6} alkyl substituted with 0-4 R^4 groups, C_{2-6} alkenyl substituted with 0-4 R^4 groups, and C_{2-6} alkynyl substituted with 0-4 R^4 groups;

alternatively, $NR^{13}R^{14}$ comprises a 3-7 membered saturated, unsaturated, or aromatic heterocycle containing the nitrogen atom to which R^{13} and R^{14} are attached and optionally containing one or more oxygen, nitrogen, and sulfur atoms;

R^{15} is selected from H, C_{1-6} alkyl, phenyl, naphthyl, and 5-6 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms;

M^B is selected from C_{1-6} alkyl substituted with 0-2 R^{16} groups, C_{2-6} alkenyl substituted with 0-2 R^{16} groups, C_{2-6} alkynyl substituted with 0-2 R^{16} groups, -CHO, $-C=N-NR^{13}R^{14}$, $-C=N-OR^{13}$, $-CH_2-NR^{13}R^{14}$, $-CH_2SR^{13}$, and $-CH_2OR^{13}$;

R^{16} is selected from C_{6-10} saturated, unsaturated, or aromatic carbocycle substituted with 0-2 R^4 groups, and 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms, and substituted with 0-2 R^4 groups;

M^C is selected from H, OH, $-OR^{13}$, and $-OC(O)-C_{1-5}$ alkyl substituted with 0-2 R^{16} groups;

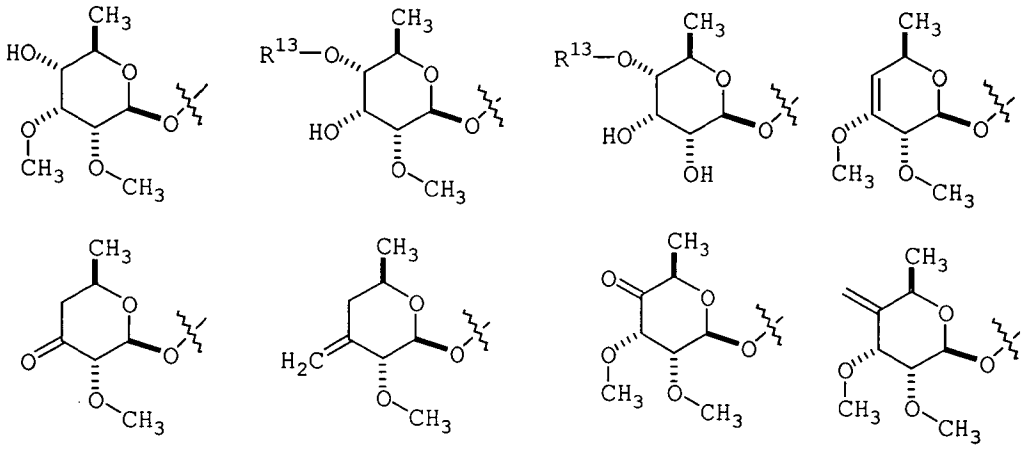
M^D is selected from H, OH, $-OR^{13}$, and $-OC(O)-C_{1-5}$ alkyl substituted with 0-2 R^{16} groups;

alternatively, M^C and M^D taken together are -O- and form an epoxide ring with the two carbons to which they are respectively attached;

M^E is selected from H, OH, R^{17}, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-O-C_{2-6}$ alkynyl, $-O-C_{2-6}$ alkynyl, $-C(O)-R^{13}$, $-C(O)-C_{1-6}$ alkylene-R^{13}, $-C(O)-C_{2-6}$ alkenyl-R^{13}, $-C(O)-C_{2-6}$ alkynyl-R^{13}, $-C_{1-6}$ alkyl-X-R^{13}, $-C_{2-6}$ alkenyl-X-R^{13}, and $-C_{2-6}$ alkynyl-X-R^{13};

X is selected from $-OC(O)-$, $-OC(O)O-$, $-OC(O)NR^{13}-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-NR^{13}C(O)O-$, $-NR^{13}C(O)NR^{14}-$, $-NR^{13}C(NH)NR^{14}-$, and $-S(O)_p-$;

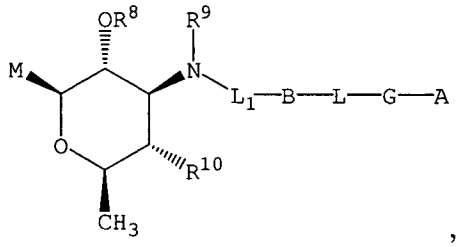
R^{17} is selected from:



; and,

M^F is selected from H, OH, $-NR^{13}R^{14}$, $-C_{1-6}$ alkyl substituted with 0-2 R^{16} groups, $-C_{2-6}$ alkenyl substituted with 0-2 R^{16} groups, $-C_{2-6}$ alkynyl substituted with 0-2 R^{16} groups, $-O-C(O)C_{1-5}$ alkyl, $-O-R^{13}$, $-O-C_{1-6}$ alkyl substituted with 0-2 R^{16} groups, $-O-C_{2-6}$ alkenyl substituted with 0-2 R^{16} groups, and $-O-C_{2-6}$ alkynyl substituted with 0-2 R^{16} groups; provided that when M^F is attached to a double bond, it is H or $-C_{1-6}$ alkyl substituted with 0-2 R^{16} groups.

2. A compound having the formula:

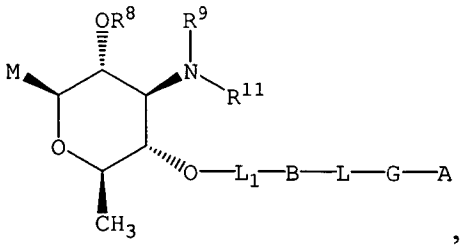


,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

A, G, L, B, L_1, M, R^8, R^9, and R^{10} are as described in claim 1.

3. A compound having the formula:

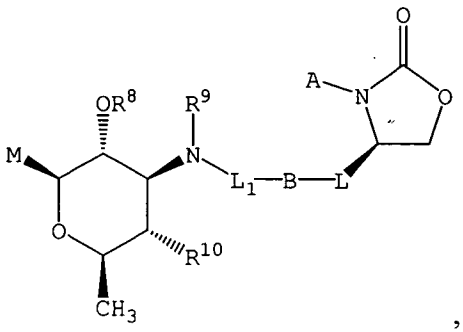


,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

A, G, L, B, L_1, M, R^8, R^9, and R^{11} are as described in claim 1.

4. A compound according to claim 1, having the formula:



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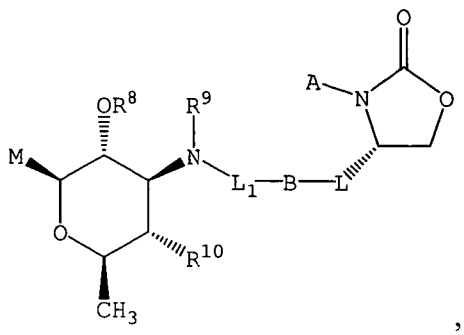

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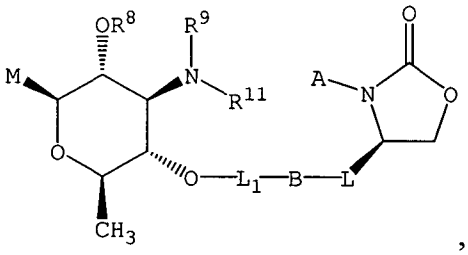
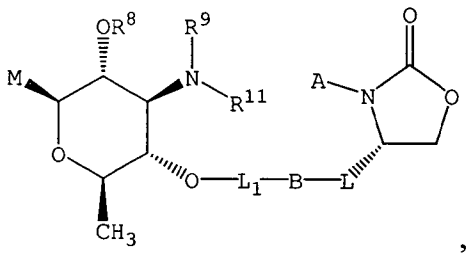


, or


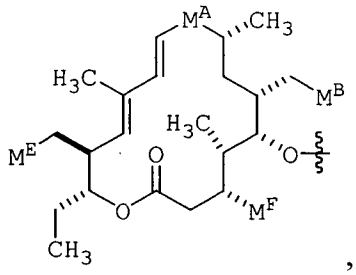
,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

B is substituted with 0-2 R^4 groups and is selected from: thiophene, furan, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5,-dihydrooxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1-tetrazol-5-yl, 2-tetrazol-5-yl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazolidine-2,4-dione, oxazolidine-2,4-dione, imidazolidine-2,4-dione, oxazolidin-2-one, thiazolidin-2-one, 3H-oxazol-2-one, 1,3-dihydro-imidazol-2-one, 1,3-dihydro-imidazole-2-thione, 2-thioxo-imidazolidin-4-one, and 4-thioxo-imidazolidin-2-one;

L_1 is selected from -C(O)CH=CH-, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2C(O)$-, -$CH_2CH_2C(O)$-, -$CH_2CH_2CH_2C(O)$-, -$C(O)CH_2$-, -$C(O)CH_2CH_2$-, -$C(O)CH_2CH_2CH_2$-, -$C(O)CH_2C(O)$-, -$C(O)CH_2CH_2C(O)$-, -$CH_2C(O)CH_2$-, -$CH_2C(O)CH_2CH_2$-, -$CH_2CH_2C(O)CH_2$-, and -$CH_2C(O)CH_2C(O)$-; and

M is selected from: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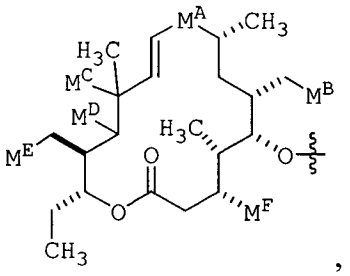
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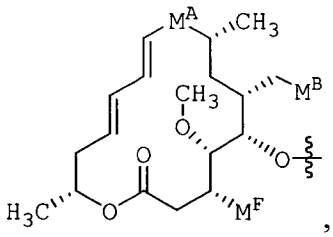
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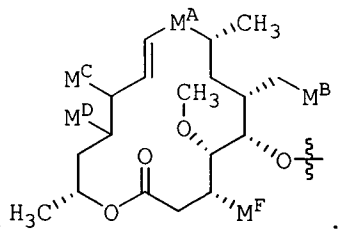
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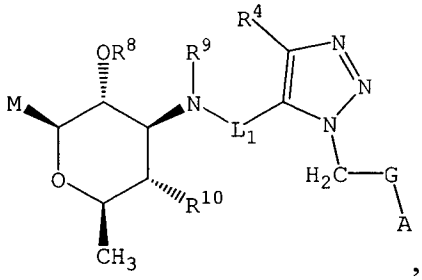
5. A compound according to claim 2 having the formula: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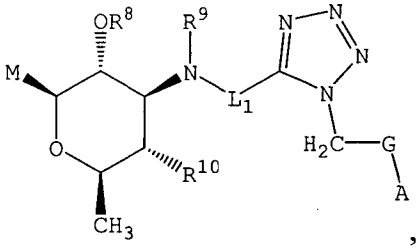
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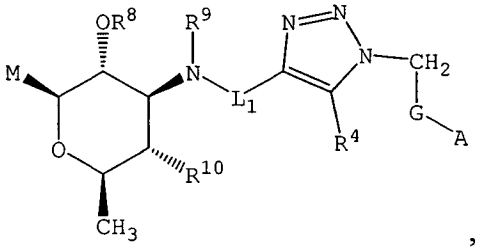
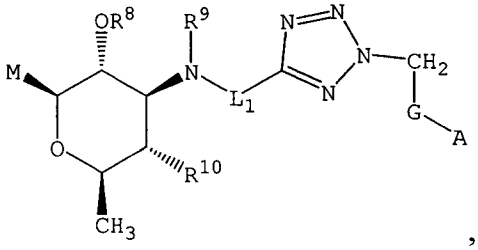
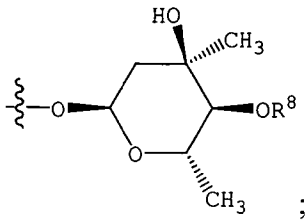

, or

,

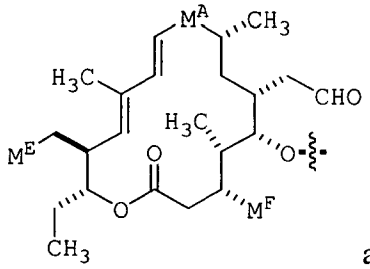
or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

R^{10} is selected from OH and:

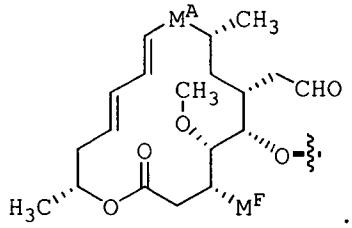


; and

M is selected from:

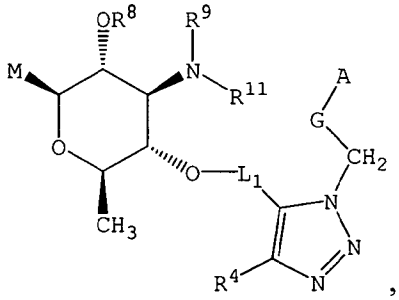


and

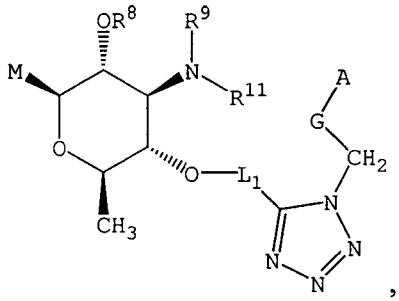


.

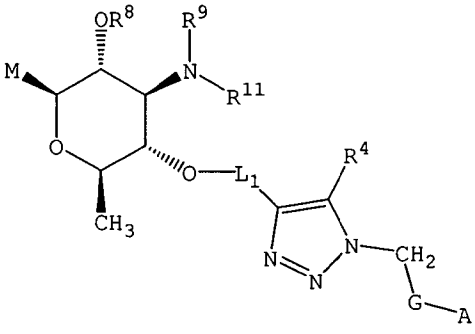
6. A compound according to claim 3 having the formula:



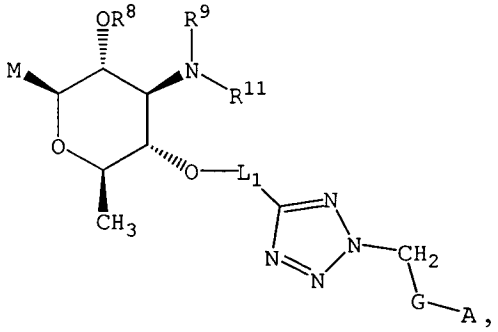
,



,



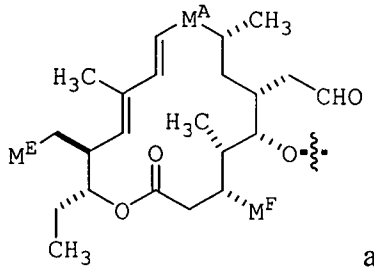
, or



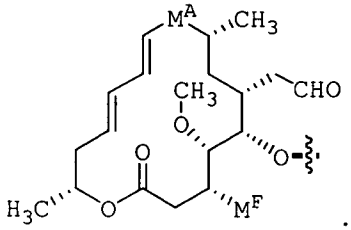
,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

M is selected from:

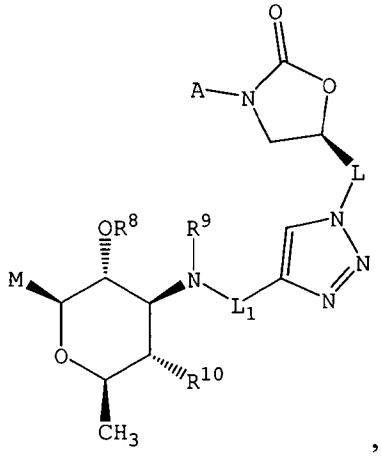


and



.

7. A compound according to claim 2 having the formula:



,

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

R^1, at each occurrence, is selected from H and F;

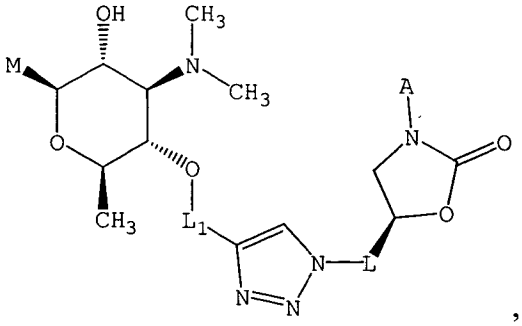
R^2 is selected from NR^3R^6, $C_{1\text{-}2}$ alkyl substituted with 1-2 R^4 groups, phenyl substituted with 0-2 R^4 groups, pyridyl substituted with 0-2 R^4 groups, morpholine substituted with 0-2 R^4 groups, imidazole substituted with 0-2 R^4 groups, and thiadiazole substituted with 0-2 R^4 groups;

R^4, at each occurrence, is selected from H, =O, F, Cl, Br, I, $C_{1\text{-}4}$ alkyl, CF_3, CN, NO_2 , NR^3R^6, $CH_2NR^3R^6$, OR^6, CH_2OR^6, $S(O)_pR^6$, $C(O)R^6$, $C(O)OR^6$, $NR^3C(O)R^6$, $C(O)NR^3R^6$, $S(O)_pNR^3R^6$, $C_{3\text{-}6}$ saturated, unsaturated, or aromatic carbocycle substituted with 0-3 R^6 groups, and a 3-6 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms, and substituted with 0-3 R^6 groups;

R^6, at each occurrence, is selected from H and CH_3; and

L_1 is selected from $-CH_2-$, $-CH_2CH_2-$, and $-CH_2CH_2CH_2-$.

8. A compound according to claim 3 having the formula:



or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

R^1, at each occurrence, is selected from H and F;

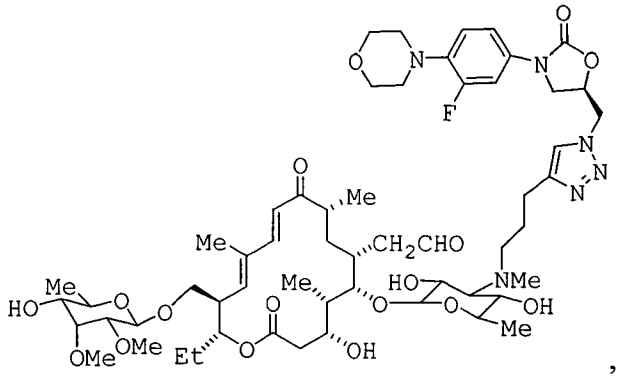
R^2 is selected from NR^3R^6, $C_{1\text{-}2}$ alkyl substituted with 1-2 R^4 groups, phenyl substituted with 0-2 R^4 groups, pyridyl substituted with 0-2 R^4 groups, morpholine substituted with 0-2 R^4 groups, imidazole substituted with 0-2 R^4 groups, and thiadiazole substituted with 0-2 R^4 groups;

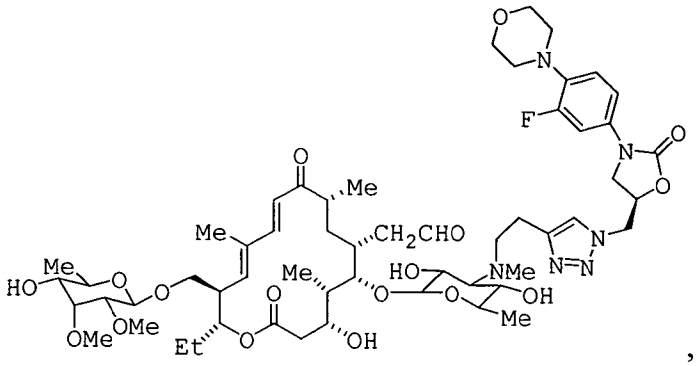
R^4, at each occurrence, is selected from H, =O, F, Cl, Br, I, $C_{1\text{-}4}$ alkyl, CF_3, CN, NO_2 , NR^3R^6, $CH_2NR^3R^6$, OR^6, CH_2OR^6, $S(O)_pR^6$, $C(O)R^6$, $C(O)OR^6$, $NR^3C(O)R^6$, $C(O)NR^3R^6$, $S(O)_pNR^3R^6$, $C_{3\text{-}6}$ saturated, unsaturated, or aromatic carbocycle substituted with 0-3 R^6 groups, and a 3-6 membered saturated, unsaturated, or aromatic heterocycle containing one or more oxygen, nitrogen, and sulfur atoms, and substituted with 0-3 R^6 groups;

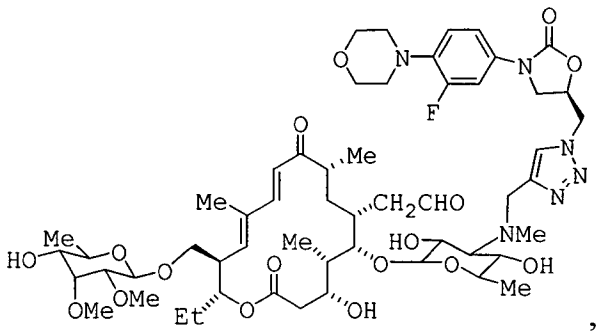
R^6, at each occurrence, is selected from H and CH_3; and

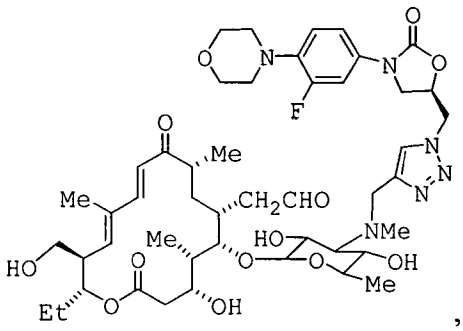
L_1 is selected from $-CH_2-$, $-CH_2CH_2-$, and $-CH_2CH_2CH_2-$.

9. A compound selected from the group consisting of:



1  ,

2  , and

3  ,

4 and a pharmaceutically acceptable salt, ester, or prodrug thereof.

5 10. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a
6 therapeutically effective amount of a compound according to any one of Claims 1-9.

7 11. A method for treating a microbial infection in a mammal comprising administering to the
8 mammal an effective amount of a compound according to any one of Claims 1-9.

9 12. A method for treating a fungal infection in a mammal comprising administering to the
10 mammal an effective amount of a compound according to any one of Claims 1-9.

11 13. A method for treating a viral infection in a mammal comprising administering to the
12 mammal an effective amount of a compound according to any one of Claims 1-9.

14. A method for treating a parasitic disease in a mammal comprising administering to the mammal an effective amount of a compound according to any one of Claims 1-9.

15. A method for treating a proliferative disease in a mammal comprising administering to the mammal an effective amount of a compound according to any one of Claims 1-9.

16. A method for treating an inflammatory disease in a mammal comprising administering to the mammal an effective amount of a compound according to any one of Claims 1-9.

17. A method for treating a gastrointestinal motility disorder in a mammal comprising administering to the mammal an effective amount of a compound according to any one of Claims 1-9.

18. A compound according to any one of Claims 1-9 for use in therapy.

19. Use of a compound according to any one of Claims 1-9 for the manufacture of a medicament for the treatment of a microbial infection, a fungal infection, a viral infection, a parasitic disease, a proliferative disease, an inflammatory disease, or a gastrointestinal motility disorder.

20. A method of synthesizing a compound according to any one of claims 1-9.

ABSTRACT

The present invention relates generally to the field of anti-infective, anti-proliferative, anti-inflammatory, and prokinetic agents. More particularly, the invention relates to a family of family of bifunctional compounds having both a macrolide-type antibiotic moiety and at least one other heterocylic moiety that are useful as such agents.

3074357

APPLICATION DATA SHEET

Application Information

Application Number::	
Filing Date::	June 1, 2004
Application Type::	Provisional
Subject Matter::	Utility
CD-ROM or CD-R?::	None
Number of CD Disks::	
Number of Copies of CDs::	
Sequence Submission?::	No
Computer Readable Form (CRF)?::	No
Number of Copies of CRF::	
Title::	Bifunctional Heterocyclic Derivatives and Methods of Making and Using the Same
Attorney Docket Number::	RIB-011PR
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	
Small Entity?::	Yes
Licensed US Govt. Agency::	
Contract or Grant Numbers::	
Secrecy Order in Parent Appl.?::	No

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Middle Name::	
Family Name::	Chen

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City of Mailing Address:: Hamden
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State or Province of Mailing Address:: CT
Country of Mailing Address:: USA
Postal or Zip Code of Mailing Address:: 06511

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State or Province of Mailing Address:: CT
Country of Mailing Address:: USA
Postal or Zip Code of Mailing Address:: 06405

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Representative Customer Number:: 021323